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FOOD SHORTAGE: AN APPEAL TO PHYSICIANS

To the Editor:—A food shortage without precedent confronts the United States. Unless there is a change for the better, the coming winter will see prohibitive high prices and consequent suffering from lack of food. The physicians of the United States, as guardians of the public health, are vitally interested because the health and the vitality of the people are at stake. It is in the power of the physicians to help relieve the food shortage by taking the lead in teaching people how to conserve the food supply. It must not be forgotten that conservation of the food supply is just as important and just as necessary as is increased production. Physicians cannot very well increase the production of foodstuffs, but on the conservation side of the problem they can be of inestimable service to the nation. It is generally recognized that people eat too much. As a nation we are more inclined toward "living to eat" than toward "eating to live." The physicians, better than any others, can discourage this habit of overeating.

Knowledge of what constitutes properly balanced rations is not widespread. Housewives have not yet had opportunity to absorb the information gained through scientific study of the food problem by experts in domestic science. The result is that the American dinner table contains much that is unnecessary and often lacks things which should be there. The physicians of the land can correct this. They can spread corrective propaganda among millions of people, and they will be heeded because of the position of trust they occupy in American families.

Correct dieting on the part of American people is of paramount importance as a measure to guard against the food stringency that faces us. We must stop the waste of food by learning how to maintain our health and strength on less than we are now consuming. In a word, I mean we must begin eating to acquire a proper amount of nourishment instead of eating just to fill up. We must make a study of the nutrition in various foods and find out what will give the amount of nourishment we really need. When we have learned these things, our housewives can begin serving us with meals that will satisfy the appetite and provide us with plenty of nourishment without entailing any waste. With the waste eliminated, the food problem will be practically solved. There is no doubt in my mind as to ability of the physicians of the nation to make themselves of prime importance in this fight to conserve the food supply. They have the necessary information and they have at their disposal the channels through which it can best be disseminated among the people of the land.

An old adage says, "Go to the busy man to get things done." Appealing to the physicians to help the food conservation movement is surely carrying out the thought in the adage. The physicians will do their "bit" for the fighting forces of the nation. We confidently expect the medical corps to outstrip their European contemporaries in solving the surgical and medical problems of the battlefield and the camp. But it is as necessary to have food as it is to have live soldiers, even in a time of war, for without food there would soon be no live soldiers. Therefore the "bit" that the physicians can do for their country is not limited to the service they can render to the army on the battlefield. They can serve the army in binding up its wounds, and they can serve the nation by showing it how to conserve food through the intelligent use of a smaller quantity than is now being consumed.

As one familiar with the food situation, I can say that the public has not yet been sufficiently impressed either with the need for more production or with the necessity for more economical handling. This is a time when one can do things that would seem presumptuous in normal times. Under that right, I call on the physicians of the United States to interest themselves in the food conservation campaign and to do all in their power to advise the public as to the imperative need for conserving, to the greatest possible degree, the food supply of the nation. By preventing waste now, we can avert hunger later on.

J. Ogden Armour, Chicago.

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ORIGINAL ARTICLES

ABNORMALITIES OF GROWTH.[1]

By Lafayette B. Mendel,

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"Throughout the animate kingdom, from the simplest microorganisms to the most complexly organized beings, that inexhaustible power of growth which ever since the genesis of the first protoplasm in the infinite past has created the structure of the fossil remains of former ages as well as our own existence—this capacity to grow, has remained as the most remarkable phenomenon of nature, the supreme riddle of life."[2]

The problems of growth have been studied in a diversity of ways, in accordance with the special training or talents of the students who have approached them as well as in response to the contemporary tendencies in the biological sciences. The very word, growth, has come to be applied with a variety of meanings. Thus we say that a crystal grows; that bacteria grow, when they multiply in number in a medium; that a tumor or a hydrocephalus grows when its mass becomes enlarged; that a child grows. Such heterogenous phenomena can scarcely be envisaged from a single viewpoint. For the present occasion, therefore, let us direct our interest primarily to man and the higher animals, in which growth may be regarded

[1] A paper presented before the Cleveland Academy of Medicine, May 12, 1916.

[2] Rubner, M., Das Problem der Lebensdauer und seine Beziehung zum Wachstum. München, 1908, p. 81; also Ernährungsvorgänge beim Wachstum des Kindes, Arch. f. Hyg., 1908, lxvi, 81.

for the most part as reduced to a minimum when the maximum average size has been reached.

Until quite recently most of the investigations of growth, in its normal as well as its pathological manifestations, have been morphological in character. This must not be interpreted as meaning that no other mode of study has been adopted. Statistics of changes in size and other features have been accumulated. Comparative analyses of growing structures have been attempted. The dynamics of the changes in growth likewise have become the subject for speculation in the past. But the dominance of the cell and its structural changes, and the popularity of cytology, embryology, cellular pathology and the newer "Entwicklungsmechanik," have overshadowed the conception of growth which realizes that increment in size means assimilation of food and the metabolism of matter. The comparative simplicity of structure of the "lower" organisms has encouraged the pursuit of the physiology of the unicellular forms in the hope that here the problems could be more easily unravelled. There is need, however, of going beyond the beginnings of the developmental processes and of supplementing the morphological methods of study. A knowledge of cell structure alone will not suffice to define growth. The size of the organism is also of much importance. "The science of nutrition," says Bayliss,[3] "would be almost impossible without the larger, warm-blooded animals. . . . . The physiology of unicellular organisms, although of considerable importance in special aspects, is not to be regarded as 'general physiology.' Indeed, if the choice had to be made between the investigation of simple or complex organisms alone, there is no doubt that a much more general and fundamental body of doctrine would be obtained from the latter."

The factors which determine the possibility of growth, and upon which, therefore, any broad generalizations regarding the abnormalities of growth must be based may be classed, with respect to the organism involved, as internal or external in character. The *internal* factors include the real impulse to grow, of whatever nature it may be; in part they are inherited, they belong to the permanent biological characteristics of the individual. Heredity, with all that it involves, determines the most potent of these internal, constitutional incentives and conditions of growth. These are the determinants which are largely beyond our immediate control, yet must be reckoned with when defects of growth appear. The *external* factors that modify growth, on the other hand, are more amenable to directive regulation. The environment as well as the food of the individual can be modified more or less at will. Here, then, is a possible point of attack. If growth implies not only a capacity to grow, but also an actual increment of body substance, there must be

[3] Principles of General Physiology, 1915, p. 291.

an accession of nutriment from without. The character of the food, its utilization and metabolism in health and in disease are open to investigation. The study of nutrition in growth therefore probably offers the most promising of all the modes of approaching an understanding of this fundamental biological process.

In order to have a common basis for the discussion of the abnormalities of growth some definition is essential, difficult though it may be to formulate one in entirely satisfactory terms. Even when the body as a whole no longer gains in size, individual parts like the hairs and nails may continue to grow. It will be preferable to speak of such phenomena of localized growth as a renewal of tissues, and likewise to exclude from the category of real growth the deposition of fat and other reserve materials that often produce a gain in weight. "Increment in size" or "gain in weight" or "enlargement of mass" are inadequate descriptions of the more specific characteristics of the growth of the higher forms. I have found no more helpful concise definition than that by Schloss,[4] who characterizes growth as "*the correlated increase in the mass of the body, in definite intervals of time, and in a way characteristic of the species.*"

Perfect growth and development implies a far-reaching *correlation* of the various parts of the body. An upset in this nicely balanced relationship is speedily recognized as an anomaly. Energy and matter are insufficient to explain the consummation and maintenance of a normal as contrasted with an abnormal composition of the cells. The *specificity* of growth is something marked, particularly when normal is contrasted with perverted growth. The definition referred to above has a particular value in the analysis of abnormalities of growth because it immediately suggests some of the anomalies or irregularities. Abnormal growth may involve (1) the correlation feature, or (2) a time factor whereby the characteristic rate of the increase in mass is not maintained. The correlation refers, for example, to the arrangement of matter in respect to composition (proportions of protein, water, etc.) and likewise to form. When there is overgrowth of one part or underdevelopment of another the correlation is upset. This is an abnormality. Likewise when the change in size is well proportioned or correlated, but unduly delayed or prolonged, growth becomes abnormal in its rate for the individual under consideration.

There is no ideal index or measure of growth. The most common statistics and perhaps the most satisfactory individual data are those obtained for the increments of body weight. The diagrams show the so-called curves of growth for man and for the albino rat—an animal closely related in many features of growth which has formed the subject of extensive investigations in recent years.

With these general characteristics of changes in weight during the

[4] Die Pathologie des Wachstums im Säuglingsalter, Berlin, 1911, p. 4.

period of growth in mind we may consider Fig. 3, page 5, which indicates in a highly schematic form some of the abnormalities in the rate of growth seen in the development of the young.

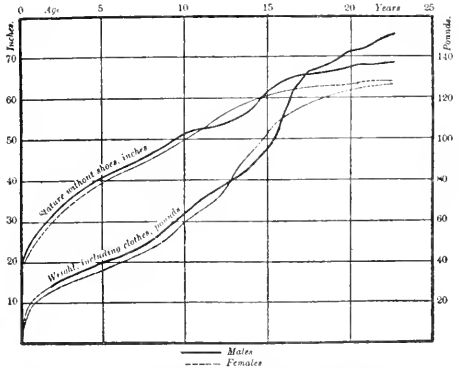

FIG. 1.—Diagram showing increase of stature and weight of both sexes, as determined by the Anthropometric Committee of the British Association. (From American Text-book of Physiology, 1896, p. 925.)

Delayed growth as the result of *external* factors can be brought about in a variety of ways associated with the food supply. Growth can be limited, of course, by an insufficient quantity of even the most appropriate food mixture. Again, there is a lower limit to

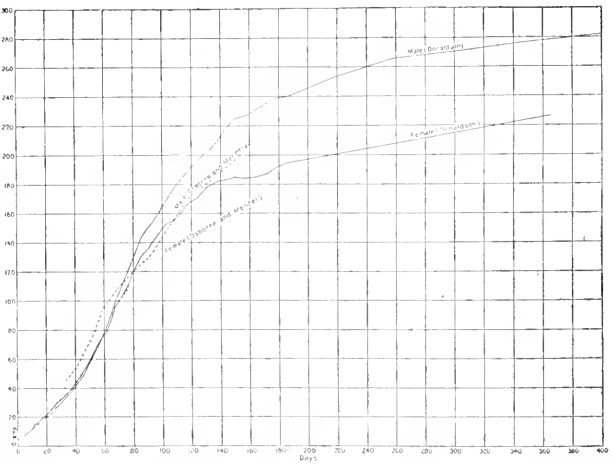

FIG. 2.—Curves of normal growth—rats. (From Osborne and Mendel and Donaldson.)

the quota of protein needed for normally rapid tissue construction, quite aside from an otherwise bountiful total energy supply. But even abundance of protein along with sufficient other nutrients may

not permit growth to continue normally, if the nitrogenous components of the diet fail to yield in suitable amounts every amino-acid required in tissue construction; for it is now an established belief among physiologists that certain of these nutrient units, such as cystine, lysine and tryptophane and doubtless others, are not constructed anew in the mammalian organism. They must be furnished as such, before new tissue containing them built up into its protoplasm can be elaborated. An appropriate supply of inorganic compounds, of lime and magnesium, of chlorid and phosphate, and perhaps of as yet unappreciated elements like iodine or manganese must sooner or later be available in the requisite minimum quantity. Finally, with all of these it now seems necessary to include a provision for the so-called food "accessories," the "vitamines" and

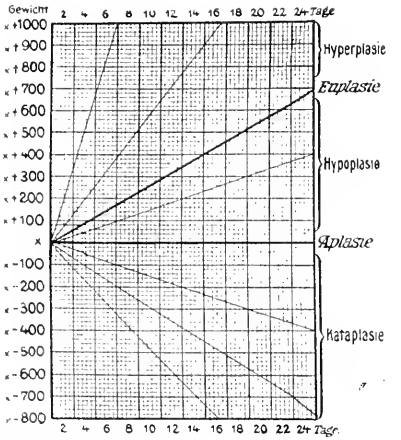

FIG. 3.—Schematic representation of abnormalities of growth. (From Schloss, Die Pathologie des Wachstums im Säuglingsalter, Berlin, 1911, p. 74.)

"auximones," which are believed to facilitate the nutrient processes and likewise, directly or indirectly, the process of growth. At any rate the failure to secure continued increment of body weight in young animals with an abundance of hitherto supposedly suitable but isolated and purified foodstuffs, and the prompt resumption of growth when very small addenda of certain natural products are furnished, leaves no other alternative than to give these accessories, seemingly insignificant though they may appear to be, due consideration in the problem of the food supply.

In discussing the nutrition of infancy Schlossmann[5] has remarked that the feeding of isodynamic quantities of food is not necessarily a guarantee of equal nutrient effects. The food must not only

[5] Beiträge zur Physiologie der Ernährung des Säuglings, Arch. f. Kinderheilkunde, liii, 1.

furnish equivalent amounts of energy, but also permit equivalent benefits to accrue to the individual that ingests it. Schlossmann therefore has suggested the term *isokerdic* (τὸ κέρδος, the gain) value to express for the equivalent biological utility of foods what the expression isodynamic indicates in respect to their comparable energy values. Repeatedly it has been observed that the addition of a seemingly insignificant amount of the non-protein, fat-free part of milk—such as the "protein-free milk" of Osborne and Mendel[6]—or of yeast (Hopkins,[7] Funk and Macallum[8]), or of plant parts containing the embryo[9] will suffice to convert failure on a given diet of isolated food substances into success. Even where one of this type of (presumably water-soluble) determinants is furnished growth may cease until some natural fat like butterfat, egg fat, or cod liver oil or

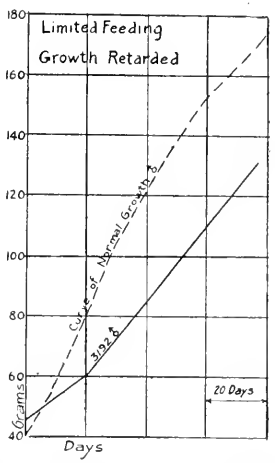

FIG. 4.—Curve of retarded growth due to limited feeding. (From Osborne and Mendel.)

fractions thereof are added to the diet. Essentials for growth that cannot be synthesized by the growing organism itself must be available in adequate amounts if the gains are to be normal in respect to the rate of growth—the time factor.

A few graphic illustrations of slow growth, exhibited in the form of curves of body weight and attributable to some of the various deficiencies of diet just discussed, are presented here. The first of these, Fig. 4, shows the effect of underfeeding with a qualitatively adequate food, in the case of albino rats.

[6] Carnegie Institution of Washington, Publication 156, Part II, 1911, p. 80.

[7] Feeding Experiments Illustrating the Importance of Accessory Factors in Normal Dietaries, Jour. Physiol., 1912, xliv, 425.

[8] Studies on Growth. II. On the Probable Nature of the Substance Promoting Growth in Young Animals, Jour. Biol. Chem., 1915, xxiii, 413–421.

[9] McCollum, E. V., and Davis, M., The Essential Factors in the Diet During Growth, Jour. Biol. Chem., 1915, xxiii, 231–246.

Fig. 5 shows the results of diets low and high respectively in the same protein.

In Fig. 6 the deficiency is exemplified by a low content of inorganic salts.

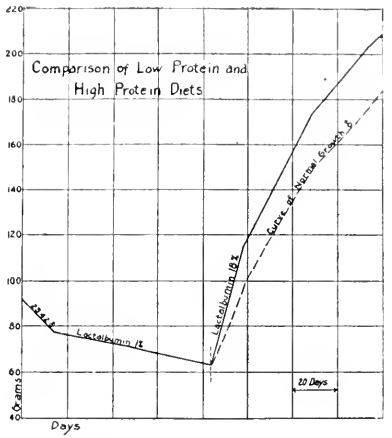

Fig. 5.—Curve showing comparative effects of diets, high and low respectively, in the same protein. (From Osborne and Mendel.)

The retarded growth, with final cessation of increase in size, seen in Fig. 7, is attributable to the lack of suitable "food accessories" in the diet.

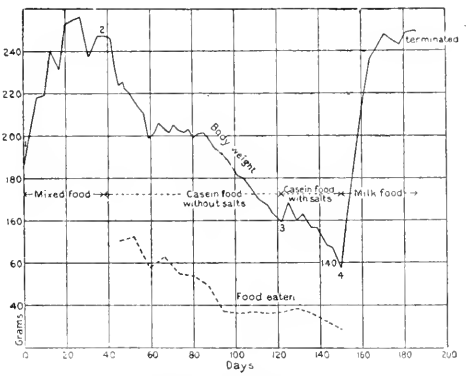

Fig. 6.—Showing effect of deficiency of inorganic salts in the diet upon growth. (From Osborne and Mendel.)

In Fig. 8 responsibility for the slow growth observed rests upon the character of the proteins fed, which failed to yield all of the amino-acids in suitable abundance.

In the preceding illustrations the growth manifested by the animals has usually been uninterrupted though proceeding at a decidedly slower rate than is normal for the species. Similar experi-

ences are familiar in the clinic for infants, but it is usually impossible to relate the retardation to a known factor as has been done in the experimental cases cited. Let there be no misunderstanding in the sense that we are attempting to refer all retardations of growth to external or dietary factors. It is merely this type of abnormality in the time relations or rate of growth that concerns us here for the moment.

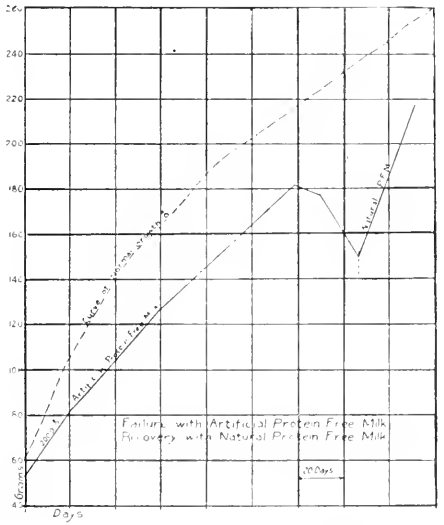

FIG. 7.—Showing effect of lack of suitable "food accessories" in the diet upon growth. (From Osborne and Mendel.)

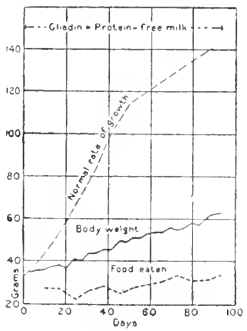

FIG. 8.—Showing failure to grow on a diet containing gliadin as the protein component. (From Osborne and Mendel.)

Complete cessation of growth in individuals not fully grown up may represent a more aggravated deprivation of some food factor essential for tissue construction—a status in which there is neither gain nor loss of weight. Such failure to grow may be observed

not only where the food supply is scanty but even where the energy content of the diet is evidently liberal. Some of the instances of "stunting" which Osborne and I have observed in our experiments with rats have been surprising in respect to the duration of the period of failure to grow. Illustrations of different types of "stunting" are shown in the following charts:

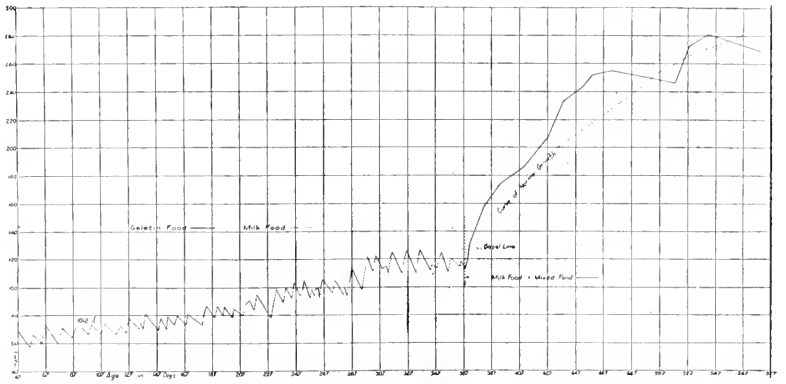

FIG. 9.—Showing prolonged failure to grow owing to inadequate character of the ration. (From Osborne and Mendel.)

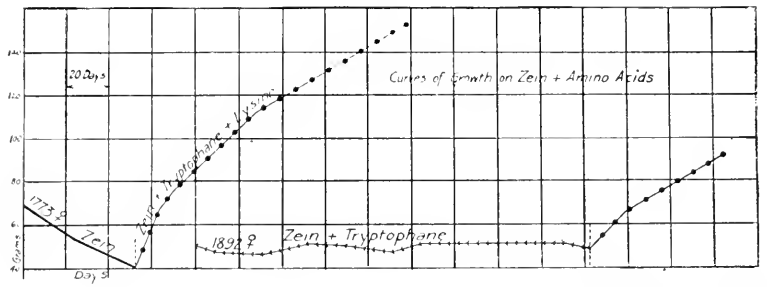

FIG. 10.—Showing failure to grow owing to a lack of the amino-acid lysine in the diet. (From Osborne and Mendel.)

Examples of this type of abnormality of growth could also readily be collected from human experience, although an equally long duration of the suppression of growth in terms of the total span of life has probably never been recorded for man. In the charts just presented it will be noted that growth was resumed in every case when an *external* factor, the diet, was altered. We are dealing here with retention of infantile characters and the capacity to grow, in many of the cases cited, at a period long beyond that at which growth is usually completed. The resumption and completion of growth after long-continued failure to grow may seem surprising in view of the wide-spread impressions that the growth impulse declines with

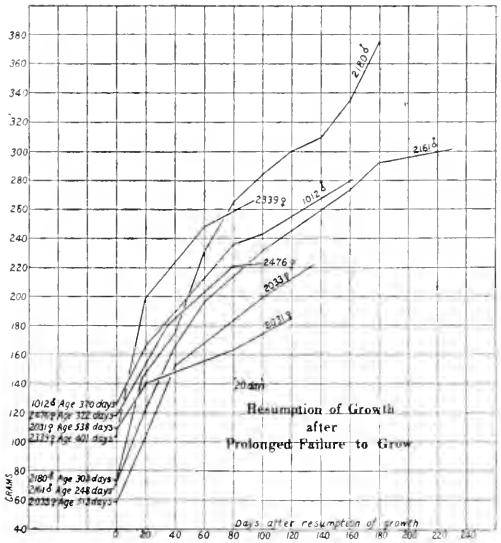

FIG. 11.—Showing resumption of growth in rats after prolonged period of suppression of growth. (From Osborne and Mendel.)

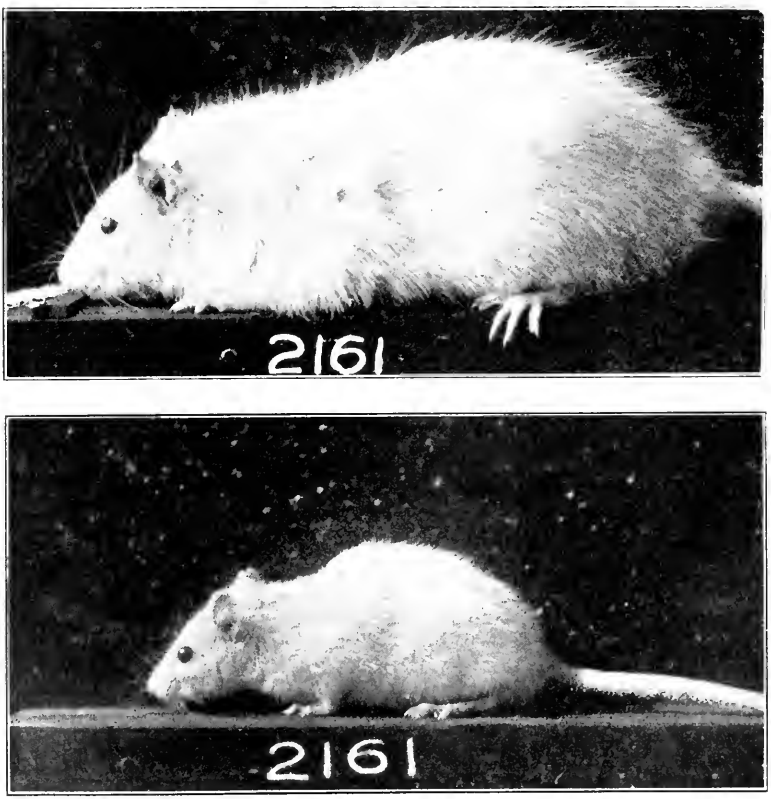

FIG. 12.—Photographs of a rat in which growth was suppressed for many months and then resumed. (From Osborne and Mendel.)

age. A few records are graphically represented in Figs. 11 and 12. The record of an infant showing a very brief delay in growth is given in Fig. 13.

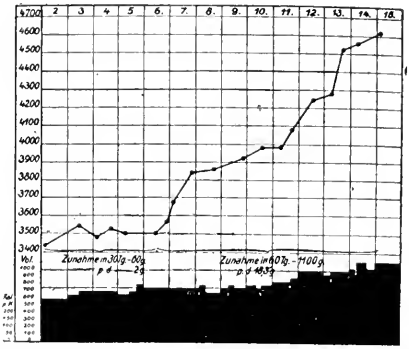

FIG. 13.—Showing the curve of suppression and resumption of growth in an infant. (From Langstein und Meyer, Säuglingsernährung und Säuglingsstoffwechsel, 1910, p. 68.)

The results of our investigation in this field have been summarized as follows:

"The growth impulse, or capacity to grow, can be retained and exercised at periods far beyond the age at which growth ordinarily ceases. In the case of our experimental animals, albino rats, in which increment of body weight ordinarily ceases before the age of 300 days, resumption and completion of growth were readily obtained at an age of more than 550 days. It is now reasonable to ask whether the capacity to grow can ever be lost unless it is exercised.

"Even after *very prolonged* periods of suppression of growth, the rats can subsequently reach the *full size* characteristic of their species. In this respect there is no impairment of the individual.

"The satisfactory resumption of growth can be attained not only after stunting by underfeeding, but also after the cessation of growth which results when the diet contains proteins unsuitable for the synthetic processes of growth or is low in protein.

"Growth in the cases referred to is resumed at a rate normal for the size of the animal at the time. It need not be slow, and frequently it actually exceeds the usual progress.

"The size or age at which the inhibition of growth is effected does not alter the capacity to resume growth. Even when the suppression of growth is attempted for very long periods at a very small size (body weight) the restoration may be adequate when a suitable diet is furnished.

"The procreative functions are not necessarily lost by prolonged failure to grow before the stage of development at which breeding ordinarily possible.

"The period of growth may be greatly prolonged by inadequacies in the diet, so that growth becomes very slow without being com-

pletely inhibited. Though the time of reaching full size is thus greatly delayed, growth, as expressed by suitable body weight, can ultimately be completed even during the course of long-continued retardation.

"The methods of partially retarding or completely suppressing growth are too varied and unlike to permit final answers as yet regarding the outcome of all of the procedures of inhibition for the subsequent welfare of the individual. Our observations apply to the effects upon size and a few other incidental features mentioned. Although it is doubtful whether the fundamental features will be altered, far reaching dogmatic statements are scarcely justifiable until the experiments have been extended to include other factors and animal species."[10]

Loss of weight, or *negative growth*, as it has been termed, is familiar not only as a manifestation of specific disease, but also as the result of malnutrition of dietary origin. Here, too, altered food supply may bring restoration of normal conditions. The "curve of repair" is unique in the rate at which changes in weight usually take place. The restoration which may follow a loss of tissues, etc., even in adult life, exceeds in its rapidity even that observed at the most vigorous periods of growth. Clinicians are well aware that recovery of weight lost during illness may take place with surprising rapidity. It seems as if the depleted body cells were ready in structure for the return of missing components without the necessity of a reconstruction of the entire fabric of the wasted tissues. A graphic expression of this is seen in Fig. 14.

Anomalies of growth expressed by an *exaggerated rate of growth* are among the rarities. Whenever the growth of an entire organism as well as that of individual organs is modified in the sense of acceleration, this usually involves repair—the reversal or return of a morbid condition to the normal as it has just been illustrated. Attention has lately been directed to the unexpectedly accelerated rate at which the increment of body weight may be resumed after growth has, for some reason or other, been inhibited for a time.[11] Fig. 15 shows that "after periods of suppression of growth, even without loss of body weight, growth may proceed at an exaggerated rate for a considerable period. This is regarded as something apart from the rapid gains of weight in the repair or recuperation of tissue actually lost. Despite failure to grow for some time the average normal size may thus be regained before the usual period of growth is ended."

Analogous conditions in infants seem to be represented by the

[10] Osborne and Mendel, The Resumption of Growth after Long-continued Failure to Grow, Jour. Biol. Chem., 1915, xxiii, 439–454.

[11] Osborne and Mendel, Acceleration of Growth after Retardation, Am. Jour. Physiol., 1916, xl, 16–20.

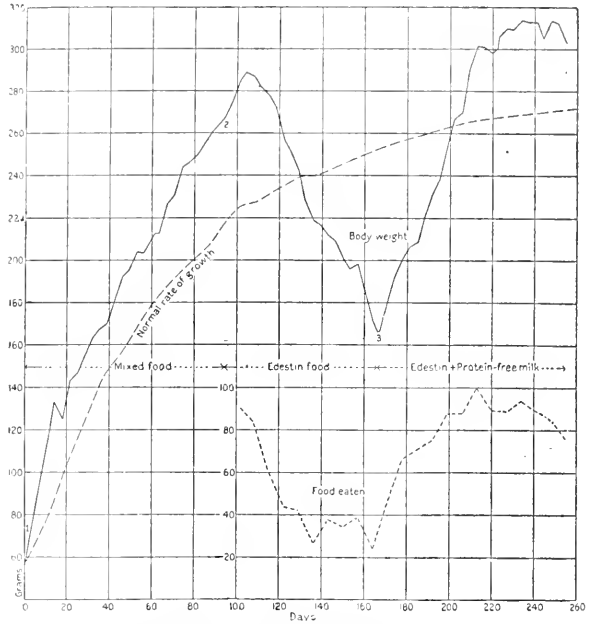

FIG. 14.—Curves showing restoration after depletion of body weight in rats. (From Osborne and Mendel.)

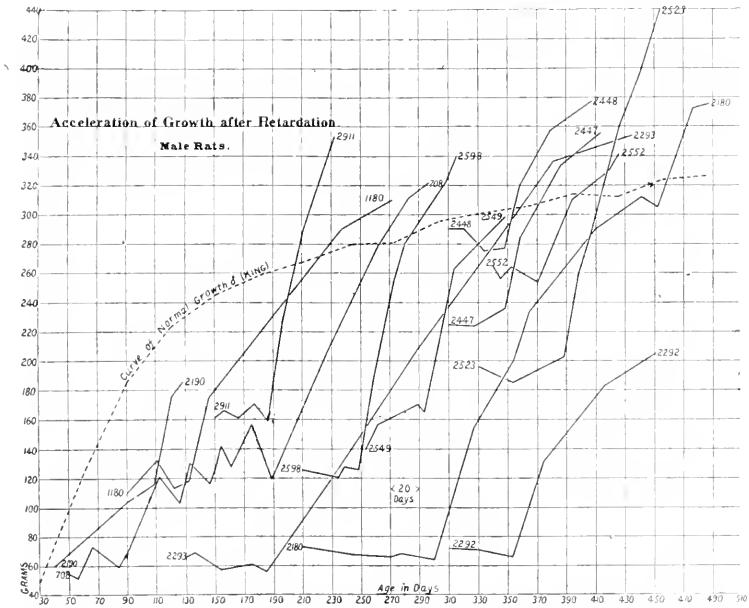

FIG. 15.—Showing curves of acceleration of growth after retardation of growth. (From Osborne and Mendel.)

following case of failure to gain weight in scurvy and the resumption of growth under the influence of orange juice added to the diet.[12]

The foregoing experiences respecting the ability of the individual to make exceptionally rapid gains of weight after periods of enforced maintenance without growth have led us to raise certain questions of broader biological interest. "What has time accomplished in the interval of unchanged total body weight? Have developmental changes or cellular rearrangements proceeded? Have some of the cells (perhaps those of certain endocrine glands) advanced in their development more nearly normally than the great mass of the tissues? If so, they might exert an undue stimulus upon the energy transformations leading to growth."[13] The inquiries here submitted may properly introduce a second phase of our subject, the *abnormalities*

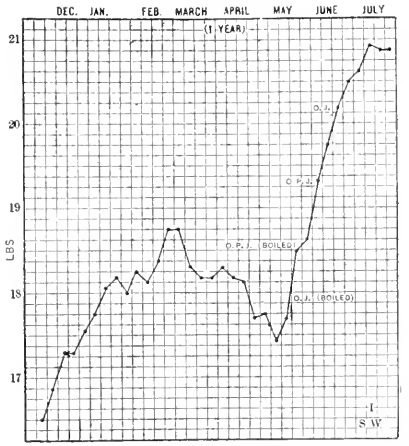

FIG. 16.—Showing curve of accelerated growth in an infant after failure to grow. (From Hess, 1916.)

of correlation in growth. The interrelations of proportion in the parts of the body may vary not only among individuals and species, but also in the same individual at different stages of development, as is shown in Fig. 17.

Precisely as there are changes in the correlation of form or morphological structure, so there may be alterations in the distribution of chemical components of the body, the upset of which represents abnormality. Thus Aron has indicated that the form of animals maintained at stationary weight before they are fully grown may change. They may grow in stature, one part changing at the

[12] Hess, A. F., The Influence of Infantile Scurvy on Growth (Length and Weight), Proc. Soc. Exper. Biol. and Med., 1915, xiii, 50.

[13] Osborne and Mendel, Acceleration of Growth after Retardation, Am. Jour. Physiol., 1916, xl, 16.

expense of another.[14] This is seen in Fig. 18, in which the same rat was photographed at intervals of forty-seven days, during which there was no increment in total weight.

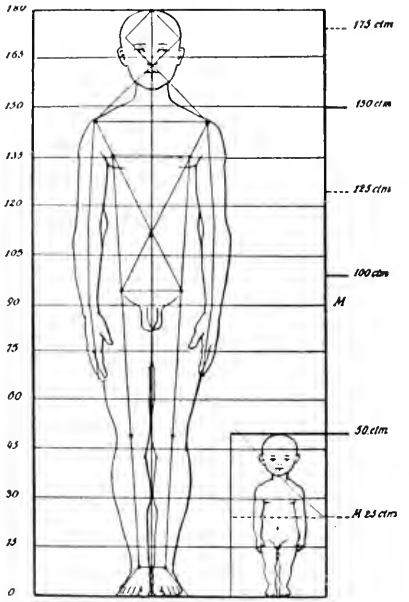

FIG. 17.—Showing changed proportions of the body of man accompanying growth. (From Stratz, Der Körper des Kindes, 1904, p. 57.)

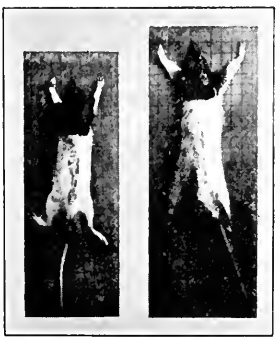

FIG. 18.—Showing changes of form with stationary body weight. (From Aron, 1912.)

The change of form noted by Waters[15] in young cattle underfed so as to keep their weight stationary is also evidence of correlative

[14] Aron, H., Weitere Untersuchungen über die Beeinflussung des Wachstums durch die Ernährung. Verhandlungen der 29sten Versammlung der Gesellschaft für Kinderheilkunde in der Abteilung für Kinderheilkunde der 84. Versammlung der Gesellschaft deutscher Naturforscher und Aerzte in Münster, 1912, 99–103.

[15] The Influence of Nutrition upon the Animal Form, Proceedings of the Society for the Promotion of Agricultural Science, 1909, xxx, 70; also XVII. Biennial Report, Kansas State Board of Agriculture, 1911, xxii, 199.

changes. Apparently the skeleton has grown in these cases at the expense of other parts. It is doubtless true, as Aron has indicated, and as has been shown in unpublished experiments by Dr. Judson in the writer's laboratory, that the inorganic components of the skeletal parts may continue to increase while the body, as a whole, is failing to gain in weight.

Defective bone growth is undoubtedly concerned in a variety of abnormalities of development. A quotation from McCrudden[16] may serve to illustrate some of the problems involved:

"Another kind of condition in which bone growth is involved is dwarfism. The causes are probably many. But in one type I have observed a disturbance of calcium metabolism associated with improper development of bone. Calcium is almost absent from the urine, leading to the belief that the blood must be poor in calcium or contain it in some unusual combination. The feces are very rich in calcium, containing sometimes more than the food. There is, in fact, a flux of calcium through the feces. And in these cases the long bones fracture easily and roentgen-ray examination shows a very thin cortex. In other types there are no abnormalities of this kind. Now, as pointed out by Rubner, we can imagine two fundamental causes for the lack of growth: (1) the lack of what might be called the tendency to grow, that property which is present in young animals, but absent in adults, and (2) the absence of the material for growth. And it seems to me that in these two types we have examples of disturbances of each of these two factors. In the one the skeleton is growing as fast as the material at its command permits. We might almost say that it is growing too fast, for it is growing in length at the expense of solidity. In the other there is no such tendency to grow. There is calcium enough present to form longer bones, but there is no tendency to form them. And this kind of disturbance of bone nutrition we may refer to as a quantitative change, for the bones fail to grow in size. There are two large subdivisions of this type—one in which the tendency to grow is absent, the other in which the material for growth is not available."

There is occasion to believe that the growth of bone in the young is only one of the developmental processes under the physiological dominance, so to speak, of the endocrine or ductless glands. The thyroid, thymus, ovary, testis, hypophysis and others, furnishing inhibitory as well as facilitating factors, may be involved. The effects of removal or loss of function of some of these glands upon growth are being investigated in a more systematic manner. The results of gonadectomy are perhaps most familiar. Many of the peculiar phenomena in respect to the evolution of stature, the secondary sex characters, psychical aberrations and their deviations from the usual mode of development induced by experiments in

[16] The Nutrition and Growth of Bone, Transactions of XV International Congress on Hygiene and Demography, Washington, September 23–28, 1912.

growth find an analogue in human cases of infantilism.[17] Sexual infantilism must be differentiated from another abnormality of childhood to which Herter[18] gave the name *intestinal infantilism*. This is a pathological state marked by a striking retardation in growth of the skeleton, the muscles and the various organs and associated with a chronic intestinal infection characterized by the overgrowth and persistence of bacterial flora belonging normally to the nursling period. The chief manifestations of intestinal infantilism are: Arrest in the development of the body; maintenance of good mental powers and a fair development of the brain; marked abdominal distention; a slight or moderate or considerable degree of simple anemia; the rapid onset of physical and mental fatigue; irregularities of intestinal digestion resulting in frequent diarrheal seizures. A type of infantilism associated with poor nutrition due to the defective circulation dependent on a congenital or acquired cardiac defect (vitium cordis) is shown in Fig. 19.

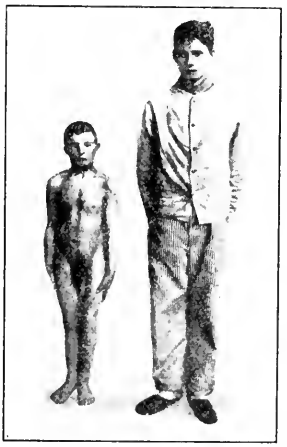

FIG. 19.—Showing infantilism in a youth, aged sixteen years, in contrast with a normal individual of the same age. (From Peritz, 1911, p. 460.)

It will be noted that the interferences with normal growth may be constitutional, or internal, in some of these manifestations of abnormalities of correlation, and external or seemingly associated with alimentation in other cases. It is not yet possible to distinguish clearly between cause and effect. Normal development of the endocrine glands (upon which in turn properly correlated growth depends) may often be conditioned upon a suitable food supply. It is thus quite conceivable, as several writers have pointed out, that the inevitable need of specific amino-acids or "food accessories" is

[17] Peritz, G., Der Infantilismus. Ergebnisse der inneren Medizin und Kinderheilkunde, 1911, xvii, 405.

[18] On Infantilism from Chronic Intestinal Infection, New York, 1908.

occasioned not alone by its value as a direct constructive unit in the growing body, but equally well because it plays some role in facilitating the function of some ductless gland. The supposed relation of iodine to the thyroid gland at once presents itself as a possible illustration. Complex pluriglandular regulatory inter-relations have often been discussed of late.

Only hasty and fragmentary reference can be made here to the more recent interesting observations of Cushing,[19] Goetsch,[20] and others on the possible relations of the pituitary gland and its disorders to growth; to the investigations of McCord[21] and of Dandy[22] on the pineal body; to the studies of Pearl,[23] Robertson,[24] and others on the feeding of pituitary and corpus luteum to growing animals.

It is too early to draw any sweeping conclusions from the already extensive literature on the ductless glands; but one may look forward with confidence to interesting developments in this field of the physiology and pathology of growth. Future investigation may show that directive influences in growth reside in the endocrine glands to an extent scarcely realized at present; possibly it will be found that the correlative factor which has been emphasized in this review is closely bound up even more closely than can now be appreciated with the proper growth and development of such special tissues.

A remarkable illustration of the potent effect of substances derived from the ductless glands has been furnished by Gudernatsch[25] and verified and extended by other investigators (Romeis[26]

[19] The Pituitary Body and its Disorders, Philadelphia, 1912.

[20] The Influence of Pituitary Feeding upon Growth and Sexual Development, Bull. Johns Hopkins Hosp., 1916, xxvii, 29.

[21] The Pineal Gland in Relation to Somatic, Sexual and Mental Development, Jour. Am. Med. Assn., 1914, lxiii, 232–235. The Pineal Gland in Relation to Somatic, Sexual and Mental Development, second paper, Jour. Am. Med. Assn., 1915, lxv, 517–520.

[22] Jour. Exper. Med., 1915, xxii, 237.

[23] Studies on the Physiology of Reproduction in the Domestic Fowl. XIV. The Effect of Feeding Pituitary Substance and Corpus Luteum Substance on Egg Production and Growth, Jour. Biol. Chem., 1916, xxiv, 123–135.

[24] Experimental Studies on Growth. III. The Influence of the Anterior Lobe of the Pituitary Body upon the Growth of the White Mouse, Jour. Biol. Chem., 1916, xxiv, 385–396. Experimental Studies on Growth. IV. The Influence of Tethelin, the Growth-controlling Principle of the Anterior Lobe of the Pituitary Body upon the Growth of the White Mouse, Jour. Biol. Chem., 1916, xxiv, 397–408.

[25] Feeding Experiments on Tadpoles. I. The Influence of Specific Organs Given as Food on Growth and Differentiation, Archiv f. Entwickelungsmechanik der Organismen, 1912, xxxv, 457–483. Feeding Experiments on Tadpoles. II. A Further Contribution to the Knowledge of Organs with Internal Secretion, Am. Jour. Anat., 1914, xv, 431–474. Feeding Experiments on Rats. III. A Further Contribution to the Knowledge of the Organs with an Internal Secretion, Am. Jour. Physiol., 1915, xxxvi, 370–379.

[26] Der Einfluss verschiedenartiger Ernährung auf die Regeneration bei Kaulquappen (Rana esculenta). I. Archiv f. Entwicklungsmechanik der Organismen, 1913, xxxviii, 183. Experimentelle Untersuchungen über die Wirkung innersekretorischer Organe. II. Einfluss von Thyroidea- und Thymusfütterung auf das Wachstum, die Entwicklung und die Regeneration von Anurenlarven, Archiv f. Entwicklungsmechanik der Organismen, 1914, xl, 571.

and Cotronei[27]). A number of mammalian organs, especially those with an internal secretion: thyroid, thymus, adrenal, testis, ovary, hypophysis, liver, muscle, etc., were given as food to tadpoles of *Rana temporaria* and *esculenta*. It was seen that each organ exerted a certain influence on growth and differentiation of the animals. Most striking was the influence of the thyroid food. It caused a precocious differentiation of the body, but suppressed further growth. The tadpoles began to metamorphose a few days after the first application of the thyroid, and weeks before the control animals did so. The influence of the thymus was quite the opposite. Especially during the first days of its application it caused a rapid growth of the animals, but postponed the final metamorphosis or suppressed it completely. The appearance of tadpoles fed on thymus and thyroid respectively is shown in Fig. 20.

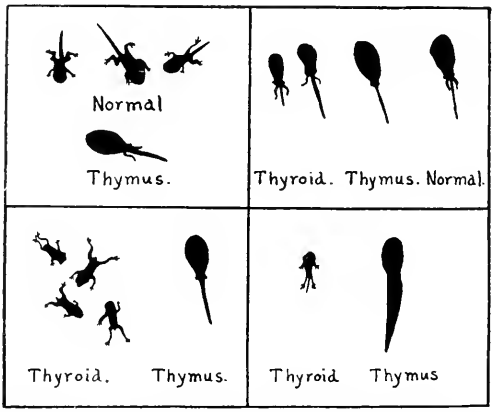

FIG. 20.—Showing effects of feeding thyroid and thymus to tadpoles.

Abderhalden,[28] from whose paper part of these illustrations are taken, has found that the thymus, thyroid, and other glands may be subjected to digestion by pepsin, trypsin, and erepsin successively, until the protein test is no longer obtainable; yet the products of digestion still contain the substances which either promote or suppress differentiation and modify growth. Combinations of several glands fed simultaneously may produce grotesque animal forms. A new field of investigation has been opened.

In the future it will be necessary to reckon with the probability

[27] Première contribution expérimentale à l'étude des rapports des organes dans la croissance et dans la métamorphose des Amphibies anoures. L'influence de la nutrition avec la thyréoide des mammifères, Archives italiennes de biologie, 1915, lxi, 305.

[28] Studien über die von einzelnen Organen hervorgebrachten Substanzen mit spezifischer Wirkung. I. Verbindungen, die einen Einfluss auf die Entwicklung und den Zustand bestimmter Gewebe ausüben, Pflüger's Arch., 1915, clxii, 99.

that growth in the sense in which we have defined it is dependent upon many factors, some of which facilitate, while others may retard the orderly progress of the process. A given environment may be disadvantageous, not only because it presents harmful or inhibitory influences, but also because it fails to manifest those that promote growth. The effect which nutrition may exert is only part of the story of growth; but it is a factor regarding which helpful information is being accumulated and one which is subject to immediate modification in a way that hereditary factors are not. Much commendable effort is being expended in improving the environment of the human individual during the period of growth. The current interest in the food hygiene of infancy, the school lunch problem, and related topics bear witness to this. These endeavors in the field of enlightened philanthropy, and public welfare should rest, as far as present-day knowledge will permit, on the basis of scientific information.

Traditions regarding growth and its perversions must give way to tested truths. It matters little if some of the determinants have not yet been discovered—if the limited experience of the laboratory fails to cover all the problems of the home and the clinic. Some real progress has been revealed, so that there is a sense of satisfaction even in relation to the obscure questions which have here been reviewed, in hearing Karl Pearson's[29] conclusion respecting the claims of science. He says: "For the present, then, it is better to be content with the fraction of a right solution than to beguile ourselves with the whole of a wrong solution. The former is at least a step toward the truth, and shows us the direction in which other steps may be taken. The latter cannot be in entire accordance with our past or future experience, and will therefore ultimately fail to satisfy the æsthetic judgment. Step by step that judgment, restless under the growth of positive knowledge, has discarded creed after creed, and philosophic system after philosophic system. Surely we might now be content to learn from the pages of history that only little by little, slowly line upon line, man, by the aid of organized observation and careful reasoning, can hope to reach knowledge of the truth, that science, in the broadest sense of the word, is the sole gateway to a knowledge which can harmonize with our past as well as with our possible future experience. As Clifford puts it, 'Scientific thought is not an accompaniment or condition of human progress, but human progress itself.'"

[29] The Grammar of Science, London, 1900.

SYPHILIS OF THE STOMACH: A CLINICAL AND ROENTGENOLOGICAL STUDY, WITH A REPORT OF TWENTY-THREE CASES.*

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The rarity of syphilis of the stomach is generally conceded, and it is largely on account of its rarity that the disease is of unusual interest. However, from my own observation and that of contemporaries it is safe to say that the condition has a greater incidence than is commonly supposed. Because of a more or less well-grounded skepticism, and because of the possibility of unfavorable criticism, the clinician is constrained to limit his reports to those cases in which the proof of the existence of the disease is most convincing. Objections to clinical diagnosis may be carried so far as to be unscientific. Evidence produced to support the specificity of the lesion in the absence of postmortem examination or microscopic study of resected tissue may be as logical and decisive as many other facts of medicine that are freely accepted.

The earlier literature of gastric syphilis has been thoroughly reviewed by recent contributors to the subject, the survey embracing the histopathological and gross anatomical descriptions and clinical classifications which constitute the basis of our present knowledge. For convenience, this literature may be divided into three periods, the first extending from the classical report of Chiari[1] in 1891 to the year 1905, the second, from 1905 to 1910, and the third, from 1910 to date. The literature of the first period deals largely with postmortem material. In that of the second period, though a number of cases are reported, the diagnosis rested largely on the history and antispecific treatment. During the third period serology and roentgenology proved useful agents in supplying the data necessary for diagnosis. In 1912, in a comprehensive review, Meyers[2] tabulated 58 cases, among which were included those reported by Birch-Hirschfeld, Fränkel, Dieulafoy, Fournier, Hemmeter, Flexner, Einhorn, Hayem, Rudnitzki and others. More recent articles dealing with the subject, and giving case reports, are those of Holitsch,[3] Mills,[4] McNeil,[5] Myer,[6] Morgan,[7] Tuohy,[8] Cronin,[9] Brunner,[10] Lensman,[11] Downes and Le Wald,[12] Brugsch and Schneider,[13] Hausmann,[14] Meuhlmann,[15] Smithies,[16] and Niles.[17] To date, our own observations have included 23 cases, a number which seems sufficiently large to warrant certain conclusions.

Symptoms and Diagnosis of Gastric Syphilis. Syphilis of the stomach, as a rule, is a late manifestation of the disease both

* Read before the American Gastro-enterological Association, Washington, May 8, 1916.

in the congenital and the acquired form, although in the former it may be present early in life. Briefly stated, the gross lesions are concerned chiefly with (1) the gumma in its various forms, and (2) diffuse syphilitic infiltration. It is generally conceded that the clinical picture as such may be much like that of non-specific gastric disease, but that usually the results obtained from therapy in the two conditions are different. Many clinicians suspect lues as the etiological factor in cases of atypical gastric disturbances that do not respond to ordinary dietetic and medical management, a suspicion very frequently justified. Heretofore no characteristic syndrome has been noted or suggested, largely because of lack of sufficient material and doubt as to whether the diagnosis of gastric syphilis was correct. In one instance, a circumscribed lesion, such as a gummatous infiltration of the pylorus, with cicatrization and resulting stenosis, may so closely simulate benign simple ulcer or even carcinomatous ulcer in all its clinical aspects as to defy differentiation. In another, owing to the presence of multiple lesions with their sequelæ or extensive involvement in one and the same organ, the symptoms presented may be so variable as to preclude proper clinical recognition or classification.

The diagnosis of syphilis of the internal organs is based usually on the past history with regard to the initial and secondary symptoms, on the demonstration of late syphilitic manifestations, Wassermann-Noguchi reactions, and the results of specific therapy. In gastro-intestinal cases the Wassermann test is the most helpful means of differentiating syphilitic ulcers, circumscribed or diffuse gummatous deposits, proliferative infiltrations and their sequelæ (cicatrices, ulceration and fibrous hyperplasia) from simple ulcers and other diseases of the stomach, particularly carcinoma. Often, however, the diagnosis of gastric syphilis is made accidentally. The absence of a history of syphilis, abortion, sterility, or a negative Wassermann reaction does not exclude the possibility of syphilis. Our own series of cases have taught us this fact plainly. On the other hand, while objective signs of active, latent, or obsolete syphilitic lesions elsewhere (in the bones, glands, skin, nasopharynx, aorta, special sense organs, stigmata) may suggest that the cause underlying the gastric disturbance is specific, such signs are usually absent or not apparent, except in cases of congenital syphilis. Of the greatest importance as indicating gastric syphilis is the combination of anacidity, subacidity, or achylia, with a syndrome approximating, but not exactly resembling, that of benign ulcer in some respects, and that of gastric carcinoma in others, and accompanied by roentgenological findings suggestive mainly of carcinoma. These factors in addition to a positive Wassermann reaction or a history of infection and other features to be mentioned later are strong presumptive evidence of gastric lues. However, the fallacy of concluding that a gastric lesion is necessarily luetic if

accompanied by a consistently positive Wassermann reaction must be avoided. The coexistence of syphilis with benign and malignant gastric disease having no obvious etiological relationship is not uncommon. On that account we have been obliged to discriminate closely in the presence of a positive Wassermann, excluding, as non-syphilitic, cases with a fairly regular syndrome, normal or increased acid values, in which the gross macroscopic appearance at the time of operation or the microscopic picture of the resected tissue was that of the usual chronic calloused gastric ulcer, and in which the improvement in gastric function was complete or satisfactory without antispecific treatment.

The criticism may be advanced that in making this distinction we have disregarded or overlooked the early uncomplicated syphilitic ulcer or circumscribed gumma, the former of which has been and is still regarded by many as the commonest form of gastric syphilis, and that, therefore, the material herewith presented represents only cases in which the disease was advanced. Such criticism is not justified by the facts to be presented herewith. The most accurate differentiation of early syphilitic gastric ulcer from non-syphilitic lesions of the stomach can be made only from the study of the symptomatology, gastric chemistry, serodiagnosis, gross pathology, roentgenology, and the results of specific therapy in both. Unfortunately our knowledge bearing on various problems of the subject is still incomplete because the cases reported have not been studied in all these phases. It may be said, however, that the role played by syphilis in the etiology of gastric ulcer is doubtful because of the following facts: (1) the rarity of cases in which the two are associated —only $\frac{1}{3}$ of 1 per cent. in our series of over 2500 operatively demonstrated cases of benign gastric and duodenal ulcer; (2) the results of Rosenow's[18] research in regard to the streptococcal origin of gastric and duodenal ulcers; (3) lack of evidence to show that simple ulcer becomes gummatous in the presence of systemic or gastric syphilis, as stated by Brugsch and Schneider.

In view of our slowly increasing knowledge with respect to the pathology of visceral syphilis in general, and gastric syphilis in particular, there is some reasonable doubt as to the frequency of uncomplicated syphilitic ulcer; moreover, when this type of lesion presents itself, other factors are invariably associated which in our experience has not made the specific nature of the lesion difficult to establish in most instances. In accordance with the original view of Klebs, Fränkel and others we recognize as actually specific only those ulcers resulting from the degeneration of a gumma. Such have been reported in considerable number in the literature, yet only one was found in Chiari's postmortem material of 98 cases. There is, however, a considerable difference in the gross pathology of benign and gummatous ulcers that is quite apparent

to the experienced surgeon or pathologist on ordinary examination. The latter are invariably multiple, have a predilection for the cardia, the lesser curvature, and especially the pyloric portion of the stomach. Usually they are associated with perigastric adhesions, proliferative hyperplasia of the gastric walls and other sequelæ resulting in gastric deformity. To the clinician and roentgenologist these characteristics in conjunction with a markedly altered chemistry rather suggest carcinoma than benign ulcus callosum.

Review of Cases. The 23 cases that have come under my observation have been either operatively demonstrated or clinically observed, and therapeutically managed in the general surgical and medical divisions of the Mayo clinic during the last seven years. With one exception all were of the acquired type of gastric syphilis.

Clinical Consideration. Sex. In the 23 cases there were 17 males (74 per cent.) and 6 females (26 per cent.) or about 3 males to each female. This is almost the sex ratio of benign chronic gastric ulcer.

Age. The youngest patient in the series was twenty, the oldest fifty-seven years. More than two-thirds were below the age of forty. The average age of both males and females was thirty-five. It will be recalled that the average age of the patients having non-malignant ulcers was forty-three years and that of cancerous patients about fifty-four.

Etiology. The number of patients admitting luetic disease was 13, or a little more than one-half. Twelve (52 per cent.) admitted repeated gonorrheal infection; in 6 the blood serum had reacted positively. This appears to be of clinical significance. The number of patients without a history of lues but having positive Wassermann reactions was 9 (40 per cent.). Of the 23 cases 17 (74 per cent.), showed positive initial Wassermann reactions in the blood serum. Three of the operatively demonstrated cases in the earliest series antedated the use of the serological test, but responded definitely to the antispecific treatment. A provocative reaction was obtained in several instances. Of the 6 female patients, all of whom were married, the disease was admitted by 2, and a premarital infection was noted in 2 others. In the case of the remainder no history was obtainable, and it is most probable that they were infected after marriage. One before marriage had given birth prematurely to a syphilitic fetus. Four reported sterility, single or repeated spontaneous abortions and tendency to amenorrhea. All were childless except 1 and this one had had two miscarriages before the birth of a healthy child. Of the married male group, several reported that their wives had had miscarriages, 2 had healthy children, and the remainder were apparently sterile.

Time of Onset of Symptoms After Infection. Definite data bearing on this feature were obtainable in 16 cases. The earliest onset was 1 year, the latest 28 years, after the disease was con-

tracted. Only 3 gave evidence of the gastric malfunction attributed to the lesion present within the 5-year period, 6 between the 5 and 10-year period, and 7 between the 10 and 20-year period. The average was 11 years.

Duration of Symptoms. The shortest duration of the symptoms on admission was 7 months, the longest 7 years. Two-thirds fell within the 2-year period. The average duration was 3+ years. In striking contrast to this is the time-element in the benign ulcer group which so uniformly averages about $12\frac{1}{2}$ years. The significance of such a brief clinical course, in view of the extensive pathological changes and altered chemistry having such direct diagnostic and prognostic bearing will be referred to later.

Clinical Course. In 9 cases the course was continuous from the outset, beginning abruptly with pain and vomiting in 2 instances, definitely intermittent in 4; intermittent, remittent or irregular in the remainder, but becoming continuous in the latter group after an average of 10 months. A distinctly progressive course was characteristic in 20 cases (90 per cent.).

Significance of Clinical Symptoms. Pain. Almost invariably the pain was described as situated in the epigastrium or pit of the stomach; in 1 instance, however, it was felt in the left hypochondrium. Dorsal radiation was noted 4 times. In 9 instances (39 per cent.) the pain was characterized as a distress; in 6 (26 per cent.) as cramping or severe; and in the remainder as dull or gnawing. In three-fourths of the cases the pain ensued immediately after eating and its duration was variable. In 4 cases it was continuous and made worse by alimentation. Definite nocturnal pain was evident in 3 cases only. In the uncomplicated gummatous ulcer-type, the pain-features simulated those of benign ulcer, being intermittent, rather periodic and delayed in appearance after meals from 1 to 3 hours. It differed from benign gastric ulcer in that anacidity was present and the pain was either only slightly relieved or not relieved at all by food or alkalies. The scirrhus or infiltrated types were associated with pain immediately after eating, which continued until the stomach had emptied itself. Such patients, to avoid discomfort, ate semisolid or liquid foods frequently and in small amounts.

Nausea. Noted definitely in only 3 instances: transient in cases with retarded motility or stenosis or associated with acute seizures.

Vomiting. This second most important symptom was noted in 19 cases (83 per cent.), and in 10 was present from the outset. In 4 cases retained gastric contents were vomited although in lesser amount than in cases of benign obstruction.

Hematemesis and Melena. Recorded in only 1 instance: single hemorrhage by mouth of 1 liter of blood. In fairly authentic cases

reported in the literature, however, severe and even fatal hemorrhages have occurred.

Flatulency. Definite complaint in 65 per cent., and present mainly for a period of one hour after taking food.

Bowel Function. Marked constipation in 50 per cent.; moderate to normal in 30 per cent. Constipation alternating with diarrheal movements in the remainder, but the former predominating.

Appetite. Characterized as good in 60 per cent.; abnormal in 10 per cent. (owing to starvation); complete anorexia or "poor" in 15 per cent.

State of Nutrition. All the patients showed marked loss in weight, over 50 per cent. having lost between 50 to 75 pounds. However, the degree of cachexia and diminished strength was mild and out of proportion to the loss in weight. This condition is converse to that which usually obtains in gastric malignancy.

Blood Estimation. Of 14 patients examined the average hemoglobin percentage was 80, average red count, 4,640,000, average white 5400.

Results of Abdominal Examination. Definite tumor or mass was absent in 20 cases (90 per cent.) and present in 1 instance (4 per cent.). In 2 cases (9 per cent.) there was a suggestion of "ridge-feel," and in all, muscle-resistance with marked or moderate tenderness. Visible peristalsis was absent in the retention cases on brief observation. Several instances are on record in which palpable epigastric tumor possessing the physical characteristics and mobility of a tumor of the stomach were associated with a history of infection and positive Wassermann reaction. However, our own inability to definitely determine that this tumor had its origin in the stomach, by all the clinical and roentgenological methods at our disposal, made it necessary to eliminate these from our series, in spite of the fact that such tumors disappeared under salvarsan and other antiseptic therapy. Hausmann has pointed out that undoubtedly it has been often erroneously assumed without more definite proof that such tumors were gastric tumors; that gumma of the liver tied off by cicatrizing contraction, or diffuse syphilitic liver-tissue tied off by cicatrized gummatous tissue may simulate tumor of the stomach.

Significance of Gastric Analysis. All of the patients, with the exception of one, who refused the tube, underwent the test. The extract usually showed poor chymification, especially that of the anacid cases, and was below normal in amount. The mucus content was not remarkable.

The small amount of gastric extract recovered in most cases was explained by the pathological conditions present. The number of patients with achylia was 18, or 82 per cent. of those examined. Four had an average of 22 per cent. free hydrochloric acid; the

average total acidity was 36 per cent. In two of these cases, achlorhydria alternated with a low hydrochloric acid content. Hypersecretion was not noted even in the retention cases which numbered 6 (26 per cent.). Blood was found in the gastric extract in 25 per cent., and occult blood was present in the feces of 17 per cent. of those examined. Lactic acid and sarcines were noted in 2 of the retention cases; in one of these Oppler-Boas bacilli were demonstrated.

A consistent achylorhydria, in fact, achylia, seems almost exclusively characteristic of luetic gastric disease. Special study has been made of gastric chemistry in syphilis of the stomach by Barbier, Robin and others, but to date no definite conclusions have been reached, owing to the variable findings. In the majority of cases in which the diagnosis was verified by postmortem examination or through the study of resected specimens the gastric analyses reported by many competent observers showed absence of free and combined hydrochloric acid. The pathology ranged from circumscribed gummatous ulcers with or without stenosis to diffuse infiltrated and contractured types. On the other hand, fairly convincing case reports by recent contributors to the subject showed the presence of free acid in normal or subnormal amounts. It is reasonable to presume that the extent and the situation of the local involvement and the systemic influence of the syphilitic virus are factors determining the gastric chemistry. However, the preponderance of evidence favors marked reduction of the gastric secretion, either through inhibition of the function of the gastric glands or atrophy of the mucous membrane. This probably has its inception in a gastritis granularis which may be a manifestation of the secondary or tertiary stage, as the direct or indirect result of the infection. Virchow recognizes an acute syphilitic gastritis which appears in the form of inflammatory infiltration, reddening of the mucous membrane, swelling, etc., and which belongs to the secondary stage. Chiari has described a diffuse and gummatous gastritis as belonging to the congenital form. In gross gastric lesions the more or less diffuse gummatous infiltration of the submucosa which finally extends to the mucosa or the diffuse syphilitic infiltrated type would at an early period affect gastric secretion. An atrophic mucosa was characteristic of all our microscopic sections. Neugebauer recently made a study of the gastric contents of 200 syphilitic recruits. Sixty-two per cent. of them were in the secondary stage and all showed definite subacidity. In 17 per cent. there was complete absence of hydrochloric acid or mere traces. Brugsch and Schneider in a review of the gastric chemistry of 100 tertiary syphilitics conclude that the frequency of achylia in tertiary syphilis in all probability is due to a chronic gastritis, and that a benign gastric ulcer in the presence of systemic tertiary syphilis is

associated with diminished secretion of hydrochloric acid. The argument has been advanced that the absence or reduction of the hydrochloric acid and ferments occurs only in advanced cases; that it is due to the rapid emptying of the gastric contents and involvement of the fundic glands, especially in the high contractured or hour-glass types. This explanation does not suffice because the same findings are present in early uncomplicated cases. Moreover, the results of my observations on acid values in benign and even malignant hour-glass stomachs, in which similar mechanical conditions surely obtain, would further seem to controvert such assumption.[19] Hausmann, who has made a critical study of 5 cases under his personal observation, regards anacidity as characteristic of syphilis. After reviewing 135 cases reported in the literature, he feels justified in considering as doubtful those cases with normal or increased secretion, and especially those incompletely studied. Patella,[20] in a review of the 140 cases of gastric syphilis he has found on record, states that the chemistry of gastric secretion was studied in only 11; in 9 of these there was anacidity, and achylia was noted in the cases especially examined. Clark,[21] in one of the more recent contributions to the subject, emphasizes the importance of gastric achylia and absence of free hydrochloric acid.

Significance of Pathology. All the cases showed deformity of variable degree, usually quite marked, with a reduction in size and contour. This was primarily the result of multiple cicatrizing gummatous ulcers or of areas of proliferative infiltration, circumscribed or diffuse, in association with perigastric adhesions. The degree of involvement was invariably in direct ratio to the duration of infection and gastric disturbance. In 4 of the 10 surgically verified cases there was definite hour-glass deformity. One patient had a stricture at the cardia, at the mid portion and at the pylorus. In all the cases the pars pylorica was the most extensively involved, although in 5 instances the involvement extended up both curvatures to the esophageal opening. In addition there was marked thickening and stiffness of the walls. The roentgenograms of two others showed hour-glass contraction, the greater loculus being above. In three instances, the ulceration and thickening seemed confined mostly to the posterior wall. In one of these cases the stomach was described as having a ruffled appearance due to the presence of multiple cicatrizing gummatous ulcers.

Grossly, there is no characteristic which readily enables the clinician to differentiate this form from some types of scirrhus carcinoma, linitis plastica, or sclerotic inflammation secondary to benign ulcer. Sailer[22] has recently called attention to this fact. The final diagnosis often rests with the exploratory laparatomy or the postmortem. However, the latter two forms are quite rare.

Microscopically, the appearance of the tissue is unlike that of

benign ulcer or carcinoma. There is usually marked atrophy of the mucous membrane, hypertrophy of the submucosa, and a thickened muscularis owing to a dense connective-tissue infiltration or fibrous hyperplasia. It is quite evident from the microscopic sections that the alteration in structure and function of the gastric mucous membrane is caused partly by a disturbance in the blood supply. The bloodvessels are invariably obliterated; in addition there is a general contracture of the surrounding tissue, the result of marked fibrosis of the submucosa and muscularis (Figs. 3d, 7a, 7b and 7c). This thickening of the submucosa and muscularis somewhat simulates linitis plastica, but everywhere there is evidence of an obliterative endarteritis and perithelial lymphocytic infiltration which is the most characteristic feature of syphilitic tissue. Although the spirochetes have been demonstrated in congenital syphilitic tissues, we were unable to find them in these acquired cases.

Gross filling defects, mainly in the lower two-thirds, suggesting extensive disease or involvement were readily apparent in the other roentgenograms. The congenital case showed a small deformed stomach, the normal portion reduced to a sac at the cardia. To the roentgenologist, the combination of gross filling defect, tendency to hour-glass deformity, absence of palpable mass and six-hour barium residue, and the absence of a proportionate cachexia, suggest gastric syphilis. Technically, however, such findings cannot be differentiated from carcinoma.

The association of syphilitic lesions or their sequelæ in other parts of the body is added proof of the specific nature of the gastric lesion. In this respect, aortitis, aneurysm and gummata of the liver or hepar lobatum were noted in several instances. Lesions of the skin and mucocutaneous junctions, hyperplasia of the lymph nodes, tibial periostitis, degenerating gumma of the chest wall, and late gummatous meningitis, were also present in individual cases. Symmers,[23] in recent postmortem studies of 314 cases of late acquired syphilis, noted the frequency of interstitial orchitis and indurative atrophy of the base of the tongue. Such instances have not been recorded in this series.

Results of Operation and Treatment. Of 10 patients operated on we were unable to get reports from 2. Three (13 per cent.) were cured and 5 (22 per cent.) were much improved. All these patients received antisyphilitic treatment in addition.

Of 13 patients not operated on, reports have been received to date from 12. Two (9 per cent.) are cured, 8 (35 per cent.), are much improved, and 2 are not improved. The total cured and improved number 16 (69 per cent.). This result exceeded expectations and is encouraging. Thorough treatment instituted during the exudative stages gives brilliant results. Advanced cases often require surgical interference because of stenosis or hour-glass deformity, the result of cicatrization or fibrous hyperplasia. If the involvement

is extensive, the result of even combined surgical and specific treatment may be disappointing. The desideratum is early diagnosis and intensive treatment.

SUMMARY AND CONCLUSIONS. 1. Syphilis of the stomach, though rare, is not as infrequent as is generally supposed. The aid of the Wassermann-Noguchi reaction and roentgen rays are necessary to establish the presence and the specificity of the lesion.

2. Denial of the disease, lack of evidence pointing to a primary lesion, or absence of positive Wassermann reaction does not exclude the possibility of gastric syphilis.

3. The diagnosis is based on a history of infection, a consistent positive Wassermann reaction, undisputable evidence of a gross gastric lesion, and—excluding cases showing irreparable extensive disease—a permanent cure by purely antisyphilitic measures. The diagnosis is often accidental. The possibility of syphilis should be considered in every atypical case, or in those not responding to ordinary methods of medical management.

4. The symptomatology which is fairly characteristic of gastric syphilis in view of the cases reported herewith, is suggestive of benign gastric ulcer; the gastric chemistry and roentgen findings rather suggest carcinoma. The average age of patients with acquired syphilis of the stomach is about 35; the duration of the complaint averages 3 years. In most instances the condition is characterized by an initial intermittent course, followed soon by continuous symptoms and associated with epigastric pain of variable degree, felt shortly after taking food and not relieved by food or alkalies. From the outset there is a tendency toward emesis, a variable degree of flatulency, good appetite, infrequency of hemorrhage and palpable tumor, diffuse abdominal resistance, a progressive course, and marked loss in weight without cachexia.

5. Anacidity or achylia is characteristic of the majority, if not of all, cases of actual gastric syphilis. This can be explained by the influence of the pathological process upon the gastric mucous membrane.

6. Extensive gastric involvement is frequently present at the time when gastric disturbance first becomes manifest.

7. A gummatous ulcer, usually multiple, and especially a diffuse syphilitic infiltration with variable degree of contracture (fibrous hyperplasia), thickening, deformity, and perigastric adhesions chiefly involving the pyloric segment, is the usual pathological condition. Demonstration of the presence of Spirocheta pallida in the resected tissue would be final proof of specificity.

8. Results from antispecific treatment are encouraging in all but very advanced cases. Surgical interference is indicated in certain cases. Early diagnosis and intensive treatment invariably result in symptomatic cure and structural improvement.

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FIG. 1.—(108061) No retention from the six-hour barium motor meal. Hour-glass stomach. Roentgen diagnosis: Syphilis or ulcer of the stomach.

Male, aged 34 years. Genital chancre, skin and mucous membrane secondaries 20 years previously. Gonorrhea three times. Gonorrheal arthritis. Chronic urethritis. Moderate alcoholism. Gastric disturbances 2 years. Cramping epigastric pains promptly after meals. Nausea and vomiting. Appetite fair. Loss of weight, 51 pounds. Liver and spleen palpable. Wassermann 3 plus. Achylia. Intravenous salvarsan four times. Mercurial inunctions and iodids. Treatment was begun July, 1914. January 5, 1915, symptomatically cured with a gain of 60 pounds. February 2, 1915, Wassermann 3 plus.

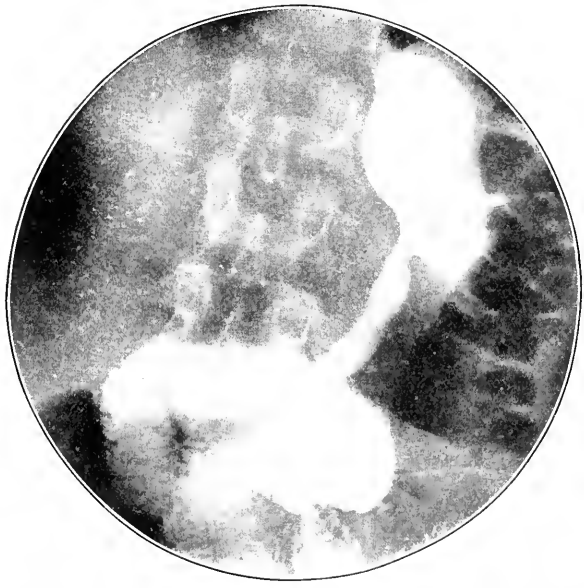


FIG. 2.—(94691) No retention from the six-hour meal. Stomach small, showing high hour-glass constriction with marked narrowing and irregularity of the pars media and pars pylorica.

Male, aged 37 years. Syphilis 9 years previously. Gastric symptoms 3 years. Epigastric pain promptly after meals, lasting one hour or longer. Continuous complaint with brief periods of remission. Pyrosis, flatulency. Loss of weight, 35 pounds. Appetite good. Wassermann 3 plus. Hyperplasia of cervical glands, epigastric resistance and tenderness. Total acids 4, no free HCl. Intravenous neosalvarsan, six times. Markedly improved. Gain of 30 pounds.

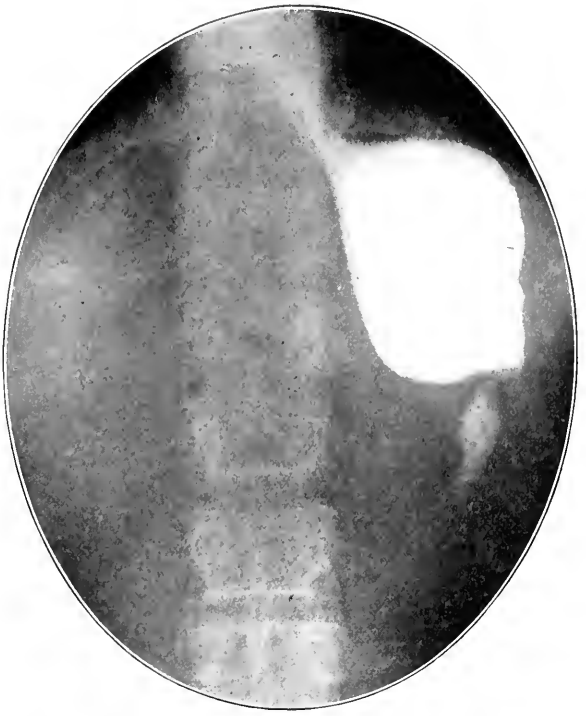


FIG. 3*a*.—(92014) Retention of one-fourth the six-hour barium motor meal. High hour-glass constriction. Reflux of the meal into the esophagus.

Male, aged 33 years. Syphilis 7 years previously. Symptoms 3 years. Epigastric discomfort due to sense of fullness and heaviness immediately after meals. Generous meal induces pain; emesis necessary for relief. Liquid diet for past 2 years. Recent vomiting of retained food material. Wassermann, total inhibition. Achylia. Salvarsan and mercury caused symptomatic improvement, but moderate pyloric obstruction persisted. Operation advised and accepted.

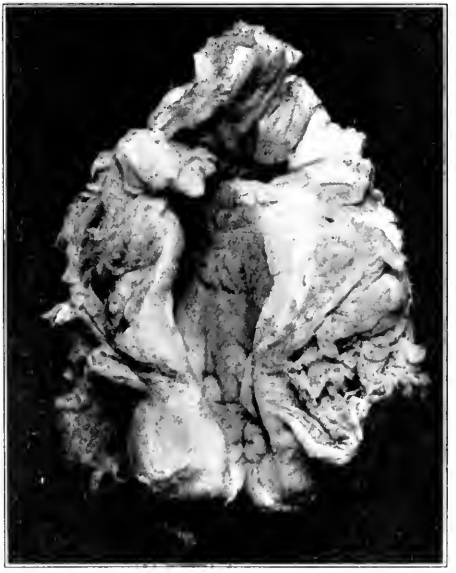


FIG. 3*b*.—(92014) Resected gross specimen. Macroscopically, the resected pyloric portion of the stomach presents a smooth uniform mucosa with three small superficial erosions. Gross section shows marked thickening of submucosa and muscularis.

FIG. 3c.—(92014) Section of tissue from stomach magnified 4 times. *A*, atrophic mucosa, curling due to fixing solution; *B*, hypertrophied submucosa; *C*, thickened musculature.

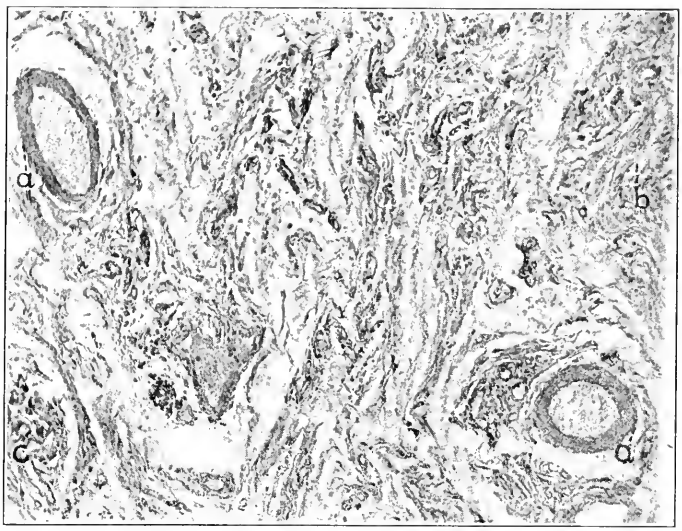


FIG. 3d.—(92014) Microphotographic section, magnified 100 times, of tissue from stomach. *A*, bloodvessels with thickened walls; *B*, dense connective tissue; *C*, nest of phagocytes. No evidence of cancer.

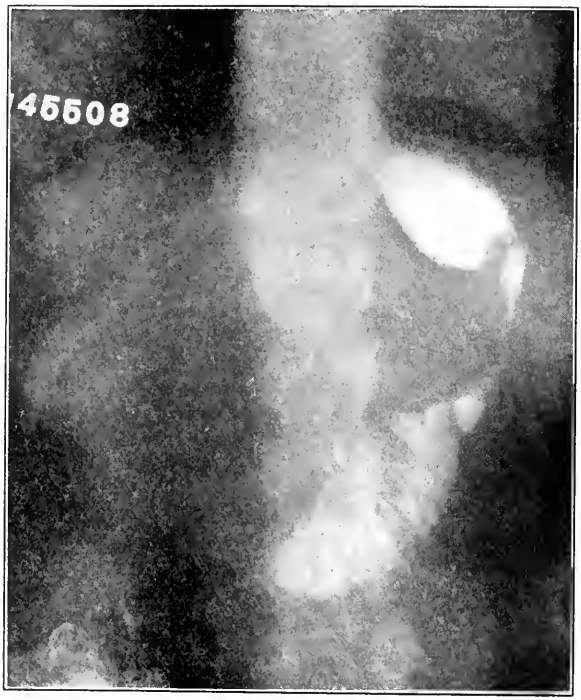


FIG. 4.—(145508) Stomach small, showing high hour-glass. Marked narrowing and irregularity of the pars media and pylorica. Pylorus gaping. No retention. Reflux of the meal into the esophagus.

Male, aged 25 years. Congenital syphilis. Exploratory operation on stomach 3 years previously. Gastric disturbances of 7 years' duration. Progressive course. Liquid or semisolid foods taken at frequent intervals. Regurgitation. Solid foods cause pain and emesis. Loss of weight 95 pounds. Numerous stigmata. Filtrate, 50 c.c.; achylia.

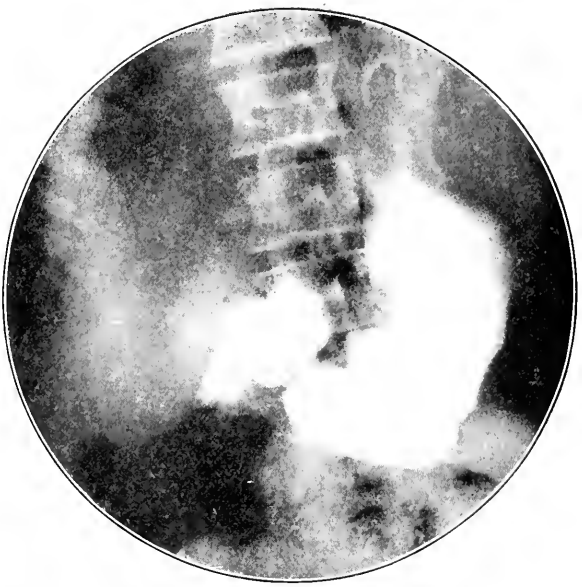


FIG. 5*a*.—(58949) Two views; First examination May 22, 1914. Roentgen examination negative.

Female, aged 27 years. Syphilis not admitted. Later it was learned that the husband was being treated for lues. Two miscarriages, one apparently healthy child. Gastric symptoms present 1½ years. Dull, heavy epigastric distress immediately after meals, lasting 10 to 15 minutes. Two or three hours later, intermittent, sharp epigastric pains radiating through to back. Quantitative food distress. Occasional emesis; flatulency, anorexia, weakness, costiveness, loss of weight. No hemorrhages. Hyperplasia of cervical glands, degenerating gummata in the region of the fifth right costo-chondral and right sterno-clavicular articulations. Total inhibition hemolysis.

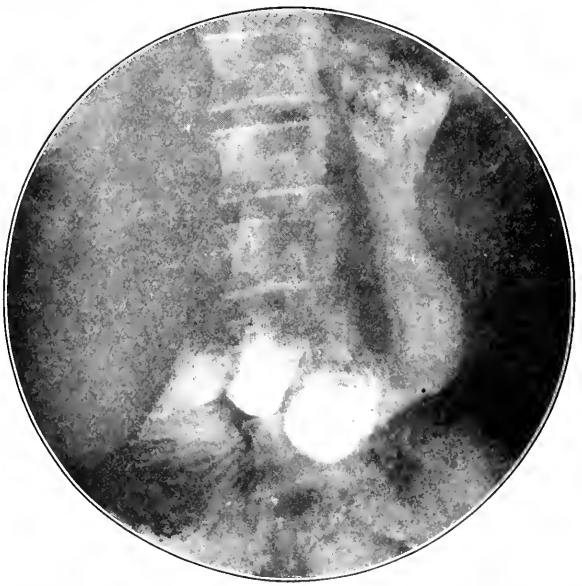


FIG. 5*b*.—(58949) Second examination August 31, 1914. No retention from the six-hour meal. Pylorus gaping. Narrowing of the pars media and cardiaca. Roentgen diagnosis: Lesion of the stomach.

Achylia. Wassermann persistently positive after repeated intravenous injections of salvarsan; but there was marked general improvement by November, 1915.

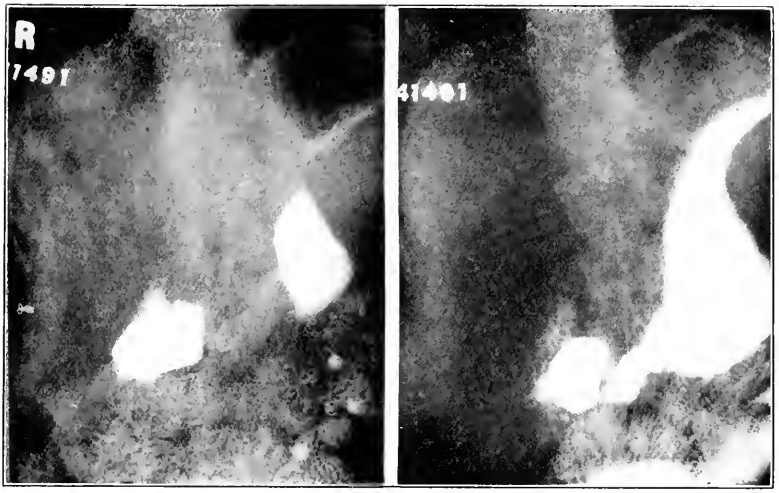


Fig. 6*a*.—(141491) Two views: September 11, 1915. No retention from the six-hour barium motor meal. Filling defect pyloric end of stomach with no corresponding palpable mass.

Female, aged 30 years. Married 3 years previously. Formerly a London barmaid. Genital chancre and oral mucous membrane secondaries about ten years previously. Two years later gave premature birth to viable syphilitic child. For one year weekly hypodermics of mercury salicylate and "pills" for two years. Gastric complaint of 8 months' duration prior to examination; epigastric discomfort soon after eating (eased by soda), even after partaking of a small meal. Gastric analysis by a local physician at outset showed absence of HCl. The acid prescribed disagreed and was voluntarily discontinued. Daily complaint. Appetite excellent. "I could eat all the time." Fresh fruits and soups seemed to agree. Chronically constipated; becoming worse. Ate small amounts frequently, but loss of weight was progressive; altogether 46 pounds. For the past month forced to vomit to relieve distress attributed to gas. Every third day regurgitation of small amounts of bitter-green fluid. Absence of diarrhea or unusual nocturnal pain (clinical signs of contracted stomach. Good color; hemoglobin 80 per cent. Epigastric resistance, but no palpable mass. Heart, lungs, etc., objectively negative. Wassermann reaction, total inhibition of hemolysis. Spinal fluid reacted negatively.

Fig. 6*b*.—(141491) Second roentgenogram taken November 27, 1915, shows marked improvement.

After the seventh intravenous salvarsan injection, and a three months' course of mercurial inunctions and potassium iodid, the reaction was strongly positive. Repeated gastric analysis showed persistent absence of free HCl; absence of peptic activity (Mettes' method) even after dilution of filtered gastric contents with $\frac{1}{20}$ normal HCl in proportion of 1 to 16. Average total acidity, 9. Symptomatically well after third intravenous salvarsan treatment. Treatment was begun September, 1915. Patient discharged as cured January, 1916. Gain of 35 pounds. Present health (May, 1916) excellent. Further antispecific treatment recommended.

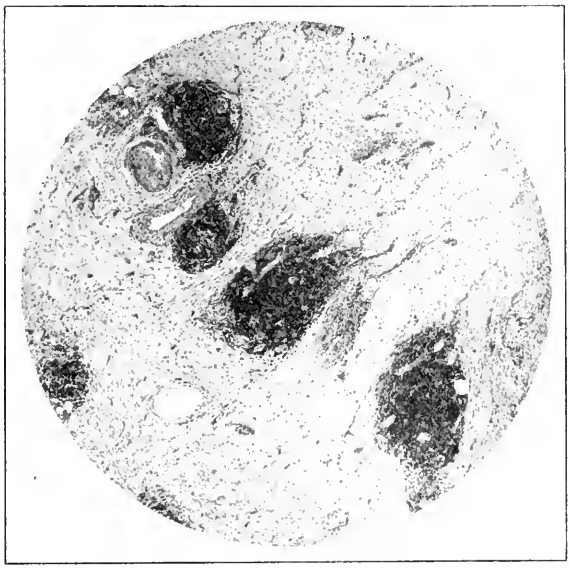


FIG. 7*a*.—(68261) Multiple groups of lymphocytes and marked fibrosis of submucosa.

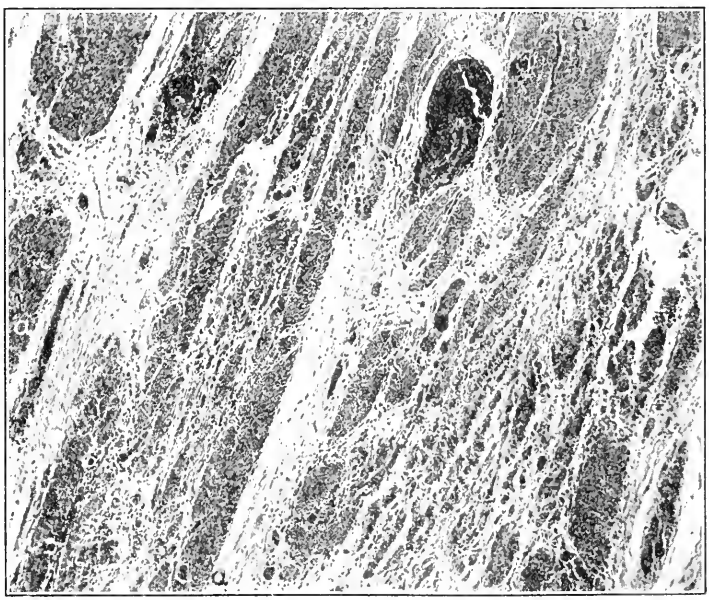


FIG. 7*b*.—(68261) (*a*) Marked fibrosis of gastric musculature.

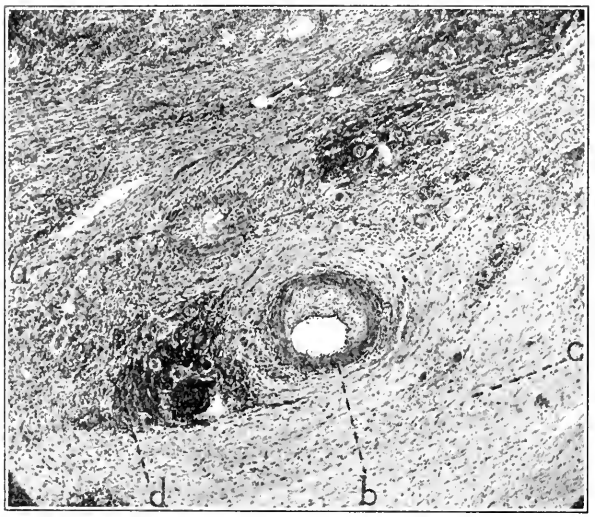


FIG. 7c.—(68261) (*a*) Obliterated bloodvessel; (*b*) partially obliterated bloodvessel; (*c*) fibrous tissue; (*d*) group of lymphocytes.

Male, aged 43 years. Lues 16 years' duration. Treated for 2 years. Gastric symptoms for 2 years and 3 months. At the outset at frequent intervals had "spells" lasting 3 or 4 days; left epigastric pain 15 to 20 minutes after meals lasting about a half hour. Trouble gradually progressive and daily pain becoming severe; also pyrosis and emesis. Acute pain seizures may last 2 to 6 hours. Absence of hyperacidity and stasis. Loss of 20 pounds in weight.

Upper abdominal resistance, tenderness in lower left epigastrium and no palpable mass. Anacidity. Preoperative diagnosis, carcinomatous gastric ulcer. On June 3, 1912, exploratory operation (W. J. Mayo): "Ulceration and thickening (3 x $3\frac{3}{4}$ cm.) on the posterior wall of the pyloric portion. Remainder of stomach above was small and hypertrophied. Syphilitic appearance." A partial resection was done. Wassermann reaction, after laparotomy, was strongly positive. Antisyphilitic treatment was given with marked improvement.

INTERMEDIARY METABOLISM IN DIABETES.

By Graham Lusk,
NEW YORK.

The phenomena of human life are dependent upon the reactions which take place between myriads of cells and their food and oxygen supply. One kilogram of body substance contains 30 grams of tissue nitrogen. The essential waste of this nitrogen amounts to 1.7 mgs. per kilogram of body substance per hour, or one part in 18,000 of that which is contained in the body. This is the wear and tear metabolism of protein at a minimal level. One may calculate that the least amount of energy which is necessary to maintain the life processes of 1 kg. of body substance is 1 calorie per hour, which represents the quantity of energy contained in 215 mgs. of glucose. It has been estimated that 1 kg. of body tissue contains cells having a total surface area of 150 square meters. Therefore, when each square meter of this cell surface is supplied with a sugar solution containing 1.5 mgs. of glucose per hour, the life of the tissue can be maintained. One can imagine how thin a film of glucose solution around the cell is necessary for the maintenance of its life. In ordinary daily life, two-thirds of the energy which supports our bodies is derived from glucose. In diabetes the power to oxidize glucose is lost. It may be interesting to inquire into the nature of the process of the oxidation of glucose.

There are two biological reactions of glucose which have long been known under the heads of lactic acid and alcoholic fermentation. In the first instance a molecule of glucose containing six carbon atoms is broken into two molecules of lactic acid, each containing three carbon atoms. In the second instance a molecule of glucose liberates two molecules of alcohol, each containing two carbon atoms and two molecules of carbon dioxide. Both of these transformations are anaërobic; that is to say, they do not require oxygen for their production.

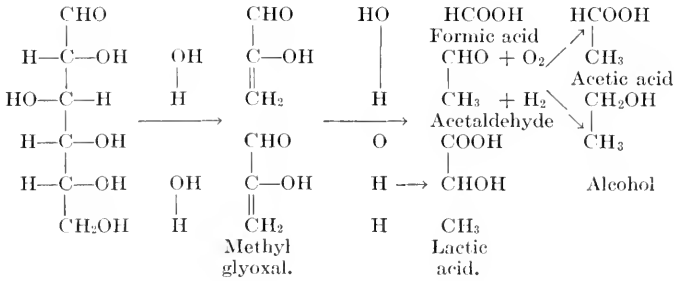
Lobrey de Brun and van Eckstein found that when glucose solutions contained even traces of hydroxyl ions, this alkalinity served to transform optically active glucose into a mixture of a multitude of other sugars, a mixture which did not rotate polarized light. This phenomenon was called mutarotation. Nef stated in 1907 that any ordinary hexose (such as glucose, fructose, galactose) when treated with weak alkali can yield in theory 116 different substances. Of these, he was able to identify 93, of which 47 were different forms of sugar, and the rest, different fragments of sugar cleavages. L. J. Henderson finds that a glucose solution undergoes mutarotation when the alkalinity of the solution is the same as that of the blood.

The presence of traces of acids prevents all these transformations. That this may have biological significance is suggested by the work of Rona and Wilenko, who found that a decrease in the alkalinity of a perfusing fluid greatly reduced the utilization of glucose by an excised, beating heart. They suggested that the diabetic condition is the outcome of a slightly acid reaction within the cells. The biological chemical reactions of sugar in the organism may be best explained by assuming that sugar is first dissociated into substances containing three atoms of carbon, such as methyl glyoxal or glyceric aldehyde. It is but a step to convert such fragments into either lactic acid or into alcohol; or to oxidize them; or by synthetic reunion to convert them into sugar once more. In the body the synthetic reunion always takes the form of glucose. After this fashion one can understand how levulose (fructose) may be transformed into glucose in the diabetic organism by the union of two intermediary substances, each containing three carbon atom chains.

Dakin, Neuberg and others have produced evidence which indicates that methyl glyoxal is an important intermediary product in sugar metabolism. Methyl glyoxal is a substance which in asphyxial conditions is readily converted into lactic acid. Biologists find that lactic acid is not oxidized. On the other hand, methyl glyoxal in the presence of oxygen readily undergoes decomposition. Neuberg has shown that the yeast cell may produce acetaldehyde from it, and that this may then be reduced to alcohol. In the presence of oxygen, however, acetaldehyde may be converted into acetic acid, which can readily be oxidized in the body into carbon dioxide and water.

The provisions in this scheme of glucose metabolism are such that if asphyxial conditions are encountered, lactic acid is produced (which may be reconstructed into glucose). Under asphyxial conditions acetaldehyde does not arise in the tissues, for if it did arise in the presence of asphyxia, alcohol would then be a product of metabolism. The prior formation of lactic acid, therefore, automatically prevents the organism from becoming a brewery.

These relations are set forth in the following formula:



In diabetes the glucose molecule appears to be invulnerable. If lactic acid or methyl glyoxal are administered they are completely transformed into glucose. If in diabetes the muscles be rendered asphyxial, by means of strychnin convulsions, no lactic acid arises from glucose, as occurs in a normal animal, which indicates that no methyl glyoxal is formed. It is conceivable, however, that after giving fructose to a diabetic animal during strychnin convulsions, some of the dissociated three carbon atom chains which are usually transformed into glucose might produce lactic acid. In complete diabetes, however, fructose is limited in its breakdown to chains of three carbon atoms, which are then convertible into glucose. The phenomena of the mutarotation of sugars in diabetes follows only one direction, and that leads to transformation into a single end product, glucose.

By the same method glucose is formed from protein. In the metabolism of protein, chains containing three carbon atoms are liberated in the organism, and these may be synthesized into glucose. The amino-acid alanin affords the simplest expression of this reaction. Alanin on hydrolysis is converted into lactic acid,

$$CH_3CHNH_2COOH + HOH = CH_3CHOHCOOH + NH_3$$

and, as shown above, lactic acid is convertible into glucose. A full analysis of these conditions has elsewhere been attempted.[1]

It has been established that in a fasting, meat-fed dog rendered completely diabetic by phlorhizin, there is a constant relation between the number of grams of urinary nitrogen and of urinary glucose. This relation is, Dextrose : Nitrogen = 3.65 : 1—and is commonly called the D : N ratio. Since 1 gram of urinary nitrogen represents the destruction of 6.25 grams of protein, it follows that 3.65 grams of glucose must have arisen from the metabolism of 6.25 grams of protein, or 58 per cent. of the molecular complex. It is well, perhaps, to place on record that this relation has been established for a man (a cancer patient) under the influence of phlorhizin and for severe types of diabetes mellitus. The following table verifies this statement, the D : N ratios being given in successive day-to-day periods:

D : N Ratios.

	Phlorhizin.		Diabetes mellitus in man				
	In dog.	In man.					
Author.	Lusk.	Benedict, S. R.	Mandel and Lusk.	Greenwald.	Foster.	Mosenthal.	Joslin.
	3.65	3.58	3.60	3.75	3.58	3.75	3.69
	3.66	3.82	3.65	3.56	3.38	3.85	3.67
	3.62	3.66	3.66	3.70	....	3.44	3.67
	3.64	3.68	3.64	3.64	3.48	3.66	3.68

[1] Lusk, Elements of the Science of Nutrition, third edition, 1917 (in press).

It may be stated, without qualification, that sugar does not arise from the metabolism of fat in the organism.

In complete diabetes the patient is, therefore, thrown upon the energy content of fat and of those fragments of protein which do not pass over into glucose for the maintenance of his life.

That this is true may be further verified by examining the respiratory quotients obtained in diabetes. It will be remembered that when glucose is oxidized in the organism, one volume of oxygen is inspired for each volume of carbon dioxide expired and the respiratory quotient is unity. When protein is oxidized the respiratory quotient is 0.8 and fat yields a quotient of 0.707. But when glucose arising from protein cannot be oxidized the respiratory quotient of protein falls to 0.63. The respiratory quotient in severe diabetes will, therefore, fall below that of fat. As a matter of fact, results have been obtained which show that the quotient observed in severe diabetes is about 0.69. The calculated "non-protein respiratory quotient" is obtained by deducting the influence which the protein metabolism would have exercised upon the observed respiratory quotient. This is found to be about 0.70 instead of 0.707, the theoretical value of fat. The "non-protein respiratory quotient" would have been higher than 0.707 if glucose had been oxidized with fat. Since the analytical methods do not allow of an accuracy greater than 1 per cent., it may be deduced that the severe diabetic subsists upon fat and those fragments of amino-acids which do not form glucose.

These results appear in the following table:

	D : N.	Respiratory quotient.	Non-protein respiratory quotient.
Phlorhizinized dog	3.54	0.687	0.704
Diabetic man (G. S.)	3.50	0.697	0.700
Diabetic man (C. K.)	3.97	0.687	0.699

It may be added that the formation of β-oxybutyric acid in the oxidation of fat likewise tends to depress the respiratory quotient unless this effect is compensated for in the expulsion of carbon dioxide from its union with bicarbonate of soda.

The heat production in diabetes does not vary greatly from that found in health unless an increased protein metabolism instigates a higher oxidation. The metabolism in severe diabetes is, therefore, finely adjusted and follows known biological laws.

THE CLINICAL SIGNIFICANCE OF THE GLUCOSE : NITROGEN RATIO IN DIABETES MELLITUS.

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PART I.—THEORETICAL AND EXPERIMENTAL.

Review of Previous Studies on the Glucose : Nitrogen Ratio. From the time it was recognized that sugar arises in the organism from protein, the relation of carbohydrate to protein metabolism has become of importance in the study of diabetes. If the maximal production of glucose from protein in total diabetics could by any means be ascertained, it is evident that a gauge of the severity of this disease would thereby be afforded. As the nitrogen of the urine is chiefly produced from albuminous substances, which also form glucose, it follows that this important question might be attacked through a study of the relation of the urinary glucose in the diabetic subject to the nitrogen elimination. Such is the reasoning underlying the large number of researches on the so-called G : N ratio[1] in diabetes.

The theory itself here involved is, however, open to question. The urinary glucose of the human diabetic, as pointed out by von Noorden,[2] cannot be certainly regarded as all which can be possibly produced within the diabetic organism, but rather only that portion of the total amount of carbohydrates escaping utilization or storage. Likewise the nitrogen of the urine may, as argued as early as 1901 by Umber,[3] by no means represent all that arises from protein katabolism, for a portion of the nitrogen so liberated may fail of excretion in the urine through its being utilized in the synthetic processes of intermediary metabolism. Still another criticism of the utility of the G : N ratio has been previously mentioned by Janney and Csonka.[4] The total amount of urinary nitrogen cannot be properly regarded as arising exclusively from sugar-producing protein. It seems then, with justice that up to the present the G : N ratio has not been regarded by clinicians as of much practical value in the treatment of diabetes.

Quite aside, however, from such theoretical objections the results of previous experimental studies on this subject present a confusing picture. Various attempts here have been made to ascertain the maximal glucose production in diabetics by means of

[1] Noorden, C. v. Handbuch d. Path. d. Stoffwechsels, Berlin, 1907, ii, 33.
[2] Handbuch d. Path. d. Stoffwechsels, Berlin, 1907, ii.
[3] Ther. d. Gegenw., 1901. [4] Jour. Biol. Chem., 1915, xxii, 203.

experiments in which proteins were administered with control of the diet. Such experiments by Rumpf, Rosenquist, Mohr and a number of others[2] have led to surprising divergent results, for they apparently show variations in the urinary G : N ratio from 0.01 : 1 to 12 : 1 or even more. Von Noorden accepts 5 : 1,[5] elsewhere 4 : 1[6] parts of glucose excreted to 1 part of nitrogen as representing maximal glucose formation from protein. The criticisms, however, which annul the value of such experiments are numerous. As they have been already discussed recently by the writer,[7] they need not be restated here.

A way out of such uncertainty seemed at first afforded by observations made on the fasting depancreatized dog, which shows a fairly constant urinary G : N ratio averaging 2.8 : 1. From this value Minkowski has calculated that about 45 per cent. of body protein is convertible into glucose. However, in another form of diabetes, that produced by phlorhizin in the dog, the G : N ratio of 3.65 : 1, corresponding to the production of 56 per cent. of glucose from protein, has been established by Lusk. Janney and Csonka,[4] on the basis of much more numerous experiments than those available to Lusk at the time of his publications, lately demonstrated that 3.4 : 1 is the more exact average fasting ratio for the phlorhizinized dog. Making due deductions for urinary nitrogen present in or originating from non-glucogenetic substances, these authors calculated that 58 per cent. body protein as a maximum can be converted into glucose. That Lusk making use of the higher ratio 3.67 : 1 also computed the almost identical glucose yield, 58.7, is to be explained by the fact that he used the uncorrected nitrogen values. If Janney and Csonka's method of calculation be employed with the 3.67 : 1 quotient, the result is an apparent glucose formation of 62 per cent. from protein. That this value is too high has been demonstrated by direct feeding experiments, to be alluded to later in this article.

Phlorhizinized animals belonging to other species, however, show strangely enough the 2.8 : 1 G : N quotient. As no adequate explanation has ever been advanced for the occurrence of both these high and low ratios in the same kind of diabetes, the actual significance of the urinary G : N ratio and also the maximal extent of glucose formation from protein has remained in doubt.

Establishment of the Glucose : Nitrogen Ratio in Complete Diabetes with the Help of Improved Methods. Evidently a new angle of attack was required for solution of the problem of determining the maximal extent of sugar formation from

[5] Noorden, C. v. Zuckerkrankheit und ihre Behandlung, Berlin, 1912, 6th edition, 16.

[6] Noorden, C. v. Disorders of Metabolism and Nutrition, New York, 1905, Part VII, 79.

[7] Janney, N. W. Arch. Int. Med., 1916, xviii, 584.

protein in diabetes. This has been afforded by studies made in our laboratory during several years past. As the methods employed have been previously described,[8] but a few words need be added here concerning their principle. Fasting dogs made completely diabetic by phlorhizin show a remarkable regularity in nitrogen and glucose excretion. Sugar ingested within certain limits as to amount is eliminated quantitatively in the urine. By careful preliminary studies we found it possible to so refine the experimental conditions that the glucose originating from ingested food substances could also be quantitatively estimated. When such experiments are properly carried out the results are surprisingly uniform. Usually they show even in extensive series of individual experiments a maximal variation of 10 per cent. or less.

With the aid of this procedure, the subject of glucose formation from protein has been extensively investigated in our later work, which has grown to the extent of a hundred or more complete metabolic experiments. Protein and muscle of various origin were fed as indicated, and the total amount of glucose arising from these materials in the completely diabetic organism ascertained. By comparing the sugar so formed to the nitrogen previously estimated in the material fed it is possible to establish the actual relationship existing between the maximal amount of sugar arising from body and other proteins in diabetes and the nitrogen content of these proteins. Thus the real protein G : N ratio could be established which differs from the urinary G : N ratio discussed above.

This new experimental method was now put to a critical test. For reasons which cannot be here detailed, in phlorhizin diabetes the glucose excreted during a fast is known to be practically entirely of protein origin.[9] In view of this, if our feeding experiments led to trustworthy results and due allowance be made for that part of the urinary nitrogen which is unrelated to glucose formation, the same amount of glucose in proportion to nitrogen should be eliminated in the urine of fasting phlorhizinized dogs as the proteins of such animals yield when fed to other phlorhizinized dogs. In both cases our experiments demonstrated that almost the same amount of glucose was formed from body proteins, which result corresponds to the protein G : N ratio of 3.6 : 1. As it has been demonstrated that sugar ingested by these animals is quantitatively excreted it is evident from the identity of these results, both that phlorhizin diabetes is a complete diabetes and that the maximal amount of sugar is formed from proteins ingested by these animals.

The successful outcome of these experiments led us to extend them to the human species and the problems presented by diabetes mellitus. By feeding human muscle to our completely diabetic dogs as done previously, it could be finally shown that the maximal

[8] Janney, N. W. Jour. Biol. Chem., 1915, xx, 321.
[9] Lusk, G. Phlorhizinglukosurie, Ergebn. d. Physiol., 1912, xxii, 315.

sugar formation from the chief body proteins of man is again 58 per cent., corresponding as in the case of the dog, to the protein G : N ratio of 3.6 : 1, the nitrogen here being protein nitrogen of the human muscle. The maximal protein G : N ratio of other species, including the ox, fish, and rabbit, was found to be about the same as for dog or man. As no difference is known to exist between sugar formation from protein in human as compared to phlorhizin mellituria, it is justifiable to apply this result to the study of diabetes mellitus. Body proteins other than muscle were found also to yield so far as studied about 58 per cent. of glucose on an average under the same circumstances. The conclusion may, therefore, be drawn that the body proteins of man collectively yield in total diabetes about 58 per cent. of glucose corresponding to the protein G : N ratio 3.6 : 1.

This quotient cannot, however, be accepted without modification as representing the maximal fasting urinary G : N ratio in diabetes mellitus, for in the urine certain of the nitrogen, as we have seen, is not properly to be regarded as arising from sugar-forming protein. This value is, however, known, and the calculation based on direct experiment could thus be made that when the urinary G : N ratio ranges about 3.4 : 1 maximal diabetes mellitus is present.[10]

Through these experimental data and deductions it is believed that former criticisms of the value of the G : N ratio lose their weight. This quotient may then be regarded as a true indication of the severity of the disease. Diabetics during a fast or on a carbohydrate-free diet may be expected to exhibit urinary G : N ratios in the neighborhood of 3.4 : 1. A number of such cases have already accumulated in which the symptoms likewise indicated the severe type of diabetes.[11] The value of this index of the severity of diabetes is then emphasized by the clinical findings. It is likely that once general attention is turned in this direction the number of such cases reported will increase.

These studies are also of importance in the question of glucose formation from fat in diabetes. As all the glucose and no more than appears in the urine of fasting diabetic subjects can be accounted for in these experiments as originating from protein, it is evident that sugar formation from fat is not extensive. This corroborates the results of the most recent researches. This matter is, however, more of theoretical interest, and need not be more than alluded

[10] Janney, N. W., and Blatherwick, N. R. Jour. Biol. Chem., 1915, xxiii, 77.

[11] Mandel, A. R., and Lusk, G. Deutsch. Arch. f. klin. Med., 1904, lxxi, 472; Lusk, G., Jour. Am. Med. Assn., July 23, 1904, 241; Allard, E. I., Arch. f. Exp. Path. u. Pharm., 1907, xvii, 1; Foster, N. B., Deutsch. Arch. f. klin. Med., 1913, cx, 501; Greenwald, I., Jour. Biol. Chem., 1913–14, xvi, 375; 1914, xviii, 115; Geyelin, H. R., and Du Bois, E. F., Jour. Am. Med. Assn., 1916, lxvi, 1532; Allen, F. M., and Du Bois, E. F., Arch. Int. Med., 1916, xvii, 1010.

to in the present connection. In this paper the clinical applications of the data are of chief importance and are discussed in the succeeding paragraphs.

PART II.—PRACTICAL APPLICATIONS.

Clinical Method of Ascertaining the G : N Ratio. Following the original suggestion of Lusk,[12] most clinicians in studying the G : N ratio have put their patients on a carbohydrate-free high protein diet. This procedure is, however, open to objection. Anyone having experience with this classical diabetic diet is forced to the conclusion that its administration is both difficult and may lead to danger for the patient. Foster,[11] also Allen and Du Bois,[11] and others, have emphasized this point.

Aside from this consideration the utility of this method of establishing the G : N ratio is subject to a further criticism. The ingestion of large amounts of protein causes a considerable augmentation in the sugar and nitrogen elimination in the urine, which in many cases may confuse the results. In rare cases of complete intolerance to carbohydrate this effect is not so apparent for the following reason. Ingested proteins of various origin, as shown by the writer and his coworkers, give rise to an average glucose production of about 60 per cent. in the completely diabetic organism, which also yields through katabolism of its own protoplasm nearly the same relative amounts of urinary glucose and nitrogen. As a result the ingestion of even large amounts of protein in the food is accompanied by no obvious change in the G : N ratio when the diabetes is complete. This is most clearly demonstrated by Lusk's experiments.[13]

When, however, incomplete diabetes exists, as is the rule, conditions are different. A certain amount of body protein is broken down and a certain amount of the resulting glucose utilized, the remainder being eliminated. The same holds true for ingested protein. If, as may happen, the full glycolytic capacity of such a milder case of diabetes is reached when all glucose possible arising from the patients own proteins has been utilized, it is clear that more glucose in proportion to nitrogen is likely to be excreted in the katabolism of protein ingested by this individual than in the case of his body proteins. The fact that a certain amount of body protein is spared by the action of albumin and fat of the food adds further to the confusion presented by the analysis of this metabolic picture.

Allard's case[14] may serve as an example bearing on this point. A diabetic was put upon a meat-fat diet alternating with fasting days.

[12] Jour. Am. Med. Assn., July 23, 1904, 241.
[13] Reilly, F. H., Nolan, F. W., and Lusk, G. Am. Jour. Physiol., 1898, i, 395.
[14] See Allard's table, modified by Lusk, G., Arch. Int. Med., 1909, 1.

Usually the lowest G : N ratios were recorded during starvation and the highest on the meat-fat days. It is probable that only on the fasting days the actual G : N ratio of endogeneous source prevailed, and that the cause of more glucose in proportion to nitrogen being excreted on the food days is as just indicated.

The only recourse, then, remaining to us in seeking to ascertain the true G : N ratio is to order a complete fast. Fortunately Allen's careful researches have demonstrated this to likewise represent the best treatment for diabetics. The G : N ratio can then readily be obtained during the initial fast. All that is necessary is a careful exclusion of food, faithful collection of the twenty-four hour urine, and nitrogen determinations in addition to glucose. As the carbohydrates of the body may become eliminated and thus increase the glycosuria during the first days of the fast and the body's capacity to utilize sugar may also vary, it is necessary to make observations during a number of successive days, five if possible. The G : N quotient after a single day's fast has little real meaning. This has been emphasized by Joslin,[15] though other recent authors on diabetes tend to consider the observation of the fasting G : N ratio for very short periods of time to be of consequence.

Proper hospital facilities are, of course, practically requisite to ascertain this index of the severity of diabetes cases, but fortunately profession and public are more and more becoming alive to the fact the glycosuric patients should at least undergo a period of study in institutions properly equipped for their care.

Clinical Significance of the G : N Ratio. The G : N ratio properly established for fasting patients is a valuable aid in the study of diabetes mellitus. In general it may be stated that the more nearly the G : N ratio ranges about 3.4 : 1, the graver becomes the prognosis. From Allen and Du Bois's article[11] which appeared during the composition of the present communication, and also states similar conclusions, the following may be quoted in this regard:

"The occurrence of the dextrose-nitrogen ratio of the phlorhizinized dog in any human patient may be taken as a sign of the gravest immediate significance. The few known to have exhibited this ratio during fasting have died, except the patient of Geyelin and Du Bois." Conversely the more nearly the G : N ratio approaches 0 : 1 the more favorable in general is the prognosis.

There are, however, a number of factors to be considered in considering the prognostic value of this index. Important among them is the rapidity of the fall of the ratio during the fast. Persistence of a high G : N ratio over a number of days bespeaks great severity of the diabetic process but fortunately is rarely observed. Again, it must be remembered that this quotient merely indicates that all the glucose arising in the katabolism of a given amount of protein fails of utiliza-

[15] Arch. Int. Med., 1915, xvi, 693.

tion and is excreted. Persistence of a high G : N ratio does not, however, necessarily indicate even a maximal breakdown of body tissue. Thus two cases may each show equally high G : N ratios, but the one individual may excrete much less glucose and nitrogen than the other. In this case the prognosis would obviously be more favorable, other factors being equal. The duration of the disease, the degree of hyperglycemia, effect of ingestion of carbohydrates on the blood sugar and the glycosuria, the severity of other clinical symptoms, and the nature of previous treatment must also be carefully considered in judging of the prognostic value of this ratio in any particular instance. This is well exemplified by the very interesting case of Geyelin and Du Bois, in which a suddenly developing complete diabetes with high G : N ratio rapidly subsided under judicious treatment. This patient also illustrates the important fact that a high G : N ratio is not without exception an indication of a fatal termination of the disease.

In several instances recently studied the G : N ratio has slightly exceeded the value 3.4 : 1. In such subjects it is probable that carbohydrate already present in the body plays a role. The excretion of this carbohydrate as glucose during the fasting periods is the very probable cause of the G : N ratios of these cases being higher than 3.4 : 1, which has been shown by our work to represent in complete diabetes the average value of this quotient for urine. It is very probable that had the fasting days in these cases having G : N ratios over 3.4 : 1 been sufficiently numerous this lower ratio would have been observed.

Summary. By means of improved experimental methods it could be established that the fasting urinary G : N ratio of severe diabetes mellitus is about 3.4 : 1. The G : N ratio is, therefore, to be regarded as a definite index of the severity of this disease. In association with other factors to be considered, the G : N ratio is a valuable prognostic sign.

OBSERVATIONS ON THE STARVATION TREATMENT OF DIABETES.

By C. F. Martin, M.D.,

and

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For the past year we have been treating all cases of diabetes admitted to the Royal Victoria Hospital, on the starvation plan.

Those patients who remained under the strict supervision, and

those who, when away, made an intelligent effort to carry out the treatment, did well, and have remained sugar-free on the prescribed diet, proved after varying periods to be suited to their tolerance.

Difficulties, however, arose with those unwilling, or unable, to follow the directions, and these difficulties, needless to say, were numerous. No doubt the supreme difficulty will always be that either the patient, or the doctor, fails to appreciate the need of strict attention to the treatment. So much precision in the diet is necessary, for severe cases, that even in the hospital routine, it has often been extremely difficult to carry out a successful treatment except with full coöperation of the patient.

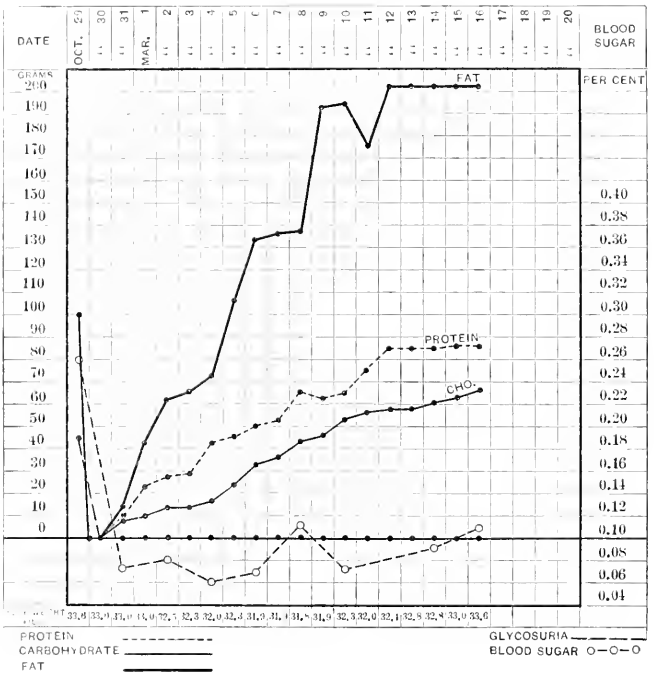

CHART I.

Again, our knowledge of the exact values of foodstuffs is still insufficient, more especially that branch relating to appreciation of the values of cooked and uncooked foods, notably the carbohydrates, and the proteins with their CHO content.

That there is greater need of standardization in our dietetic treatment is more and more apparent, and without an attempt to make clear the values of foods given, it is difficult for observers to fully coöperate in work of this nature.

The simple example may be cited of CHO values in various vegetables; while some observers compute in their estimate of CHO

food administered only the available CHO, others again include the total amount, of which unused cellulose forms a considerable portion, and alters entirely the value of our given foods. So, too, in boiled vegetables, while some compute the water in which CHO are boiled, others discard it, even though a not inconsiderable amount of available food in it should be estimated if we are to aim at exactness in our computations.

On the other hand, it is a matter of occasional surprise that patients can sometimes disregard these dietetic prescriptions with impunity. Particularly noteworthy is an instance of a patient with moderately severe diabetes, upon whom, after successful starvation treatment had conferred benefit, periodical alcoholic bouts and late nights of dissipation seemed to have no deleterious effects.

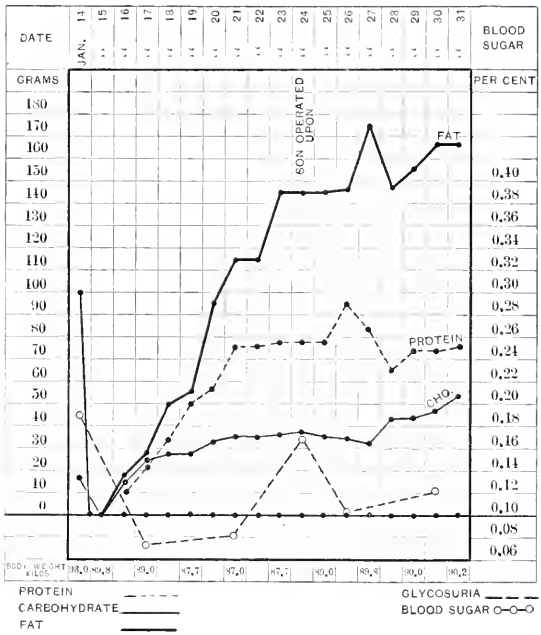

Chart II.

In two of our cases, however, fatigue and nervousness seemed to markedly aggravate an already existing glycosuria, this view coinciding with those recently emphasized by Cannon (see Chart II).

In one much-worried patient, with a glycosuria of 12 per cent., rest and relief from anxiety alone were followed by a reduction to 2 per cent. on the following day.

As a rule, one or two days of starvation sufficed to render the urine sugar-free, and in only one instance was the period as long as five days.

In the moderately severe cases it was found that patients could be raised to a tolerance of high caloric value in amazingly short time (See Chart I), but it has not seemed possible in raising the CHO tolerance to avoid the return of a hyperglycemia. In fact, in our limited experience it would seem that the metabolic disturbance which is implied by the term diabetes is not eradicated by any dietetic treatment, but merely subdued during the period of absolute precise treatment.

During the starvation treatment it was not found necessary, except in one instance, to use alcohol during the early days of treatment. In one case (Chart I), all forms of foodstuffs were raised to a very high level of value and maintained with excellent results while the patient was under supervision; but, as a rule, it was found that the more gradual and slow attaining of tolerance seemed the wiser plan, and when accompanied by a weekly starvation day the level of tolerance was raised with much greater success.

In the satisfactory cases the striking features were the speed at which sufficient satisfying food could be given, and the patient maintained upon a low level of food supply with an absence of hunger, thirst, fatigue, or loss of weight, and a general feeling of well-being seemed to exist when the proper level was maintained.

During the early treatment the loss of weight seemed rarely to be marked—in one case over 20 pounds, and in two others 13 pounds—while in the rest the loss of weight never exceeded 5 pounds. Later on the normal weight was either recovered or remained but little below the original level. Perhaps insufficient attention has been drawn to this fact, and the impression is too wide-spread that the starvation treatment is one of reduction, with severe emaciation, whereas in reality the subjective and objective evidences of starvation are not present.

Examination of Blood-sugar. The blood-sugar was periodically examined in every case. After the patient's admission an estimate was first formed of the approximate severity of the disease, together with the percentage of blood-sugar and then 100 grams of glucose were given on the first day of starvation, and the blood-sugar thereafter determined every hour for four hours.

Experience in the case of three or four patients, however, revealed the fact that four hours was an insufficient period in which properly to estimate the blood-sugar curves. We have recently extended these observations to cover twelve to twenty-four hours, and discovered thereupon that the hyperglycemia is more persistent than had been supposed.

The results by comparison with normal individuals were of great interest:

Experimental Glucose Curve of Normal Individuals. In the normal person there is, of course, an increase of blood-sugar after 100 grams of glucose have been administered, but the curve

occupies a much lower level, usually dropping below the normal in two or three hours. The maximum is attained at the end of the first hour, becomes normal again at the second hour, goes below the normal at the end of the third hour, and finally rises again to normal in four to five hours (see Chart III).

The normal threshold we regard as 0.14 per cent.

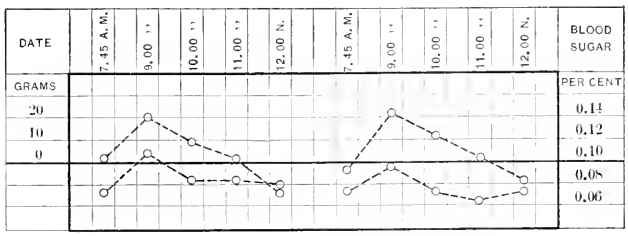

Chart III.

Experimental Glucose Curve of Diabetics. In diabetes, however, the curve was markedly altered and prolonged, as was found in repeated observations, in which, of course, we kept all individuals under exactly uniform conditions.

One hour after administration of the glucose the percentage rose, attaining its maximum at the end of the second hour, rarely at the end of the third.

The decline followed, but at a rate much slower than in normal individuals. The implication is that in diabetes, the liver not being able to hold the sugar in amount and duration as in the normal, causes a higher percentage of blood-sugar to appear.

The excursion is greater, the ascent more acute, the maximum appearing sometimes rapidly, sometimes more slowly, the variations, however, not depending on severity. As a rule, the maximum was reached at the end of two hours, and the decline was slow, occupying often eight to twelve hours (see Chart IV).

These observations seem to confirm those of Falta, who emphasized their importance in diabetes.

The abnormally slow decline in the blood-sugar curve in the later hours of the test on diabetics, possibly suggests some kind of kidney-block, and varies according to the rate of excretion, and in part, too, of course, to the degree of combustion.

Renal Block. This question of kidney-block is apparently an unsolved problem, but the more careful and repeated examinations for blood-sugar have demonstrated its importance as well as the intimate relation in many cases between glycosuria and renal function. It was found that with starvation the disappearance of the glycosuria has usually preceded the subsidence of hyperglycemia. However, our experience in one respect is at variance with Joslin,

who states that during starvation the hyperglycemia persisted, while in the majority of our cases it disappeared rapidly with starvation.[1]

With gradual increase in the diet, however, the blood-sugar rose to an abnormal degree, usually in the absence of glycosuria.

Various factors seem to play a part in inducing block, and the causes are difficult to explain; in three of our cases the values ran as high as 0.22 per cent. 0.26 per cent. and 0.28 per cent. without glycosuria. In other cases with glycosuria of long duration the block appeared, though at a lower level.

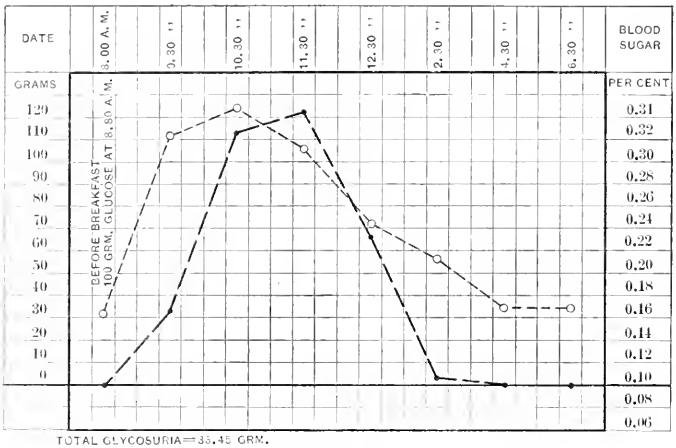

Chart IV.

A certain prognostic importance is attached to renal block in diabetes, for it would seem that the degree of hyperglycemia varies directly with the tendency to progression and the development of complications.

An insidious and progressive diabetes may often be overlooked when glycosuria is absent, and when an appreciation of the block may yield a more intelligent means of dealing with the patient.

Evidently sufficient stress is not laid upon the hour at which these estimates are made. Thus, for example, the hyperglycemia came on at first about two hours after meals, at which time we think the estimates should always be made as giving us the best guide to the diabetic changes. Blood-sugars in the majority of our diabetics were found to be normal in the early morning before breakfast, while two hours after meals a hyperglycemia was evident, this depending, of course, in part upon the diet. Often, however, when the diet was restricted in accordance with the treatment the same experience occurred.

[1] Arch. Int. Med., vol. xvi, p. 703.

The following figures will indicate the differences: Before breakfast: 0.11 per cent., 0.10 per cent., 0.18 per cent. After breakfast: 0.15 per cent., 0.16 per cent., 0.24 per cent.

Renal Glycosuria and Block. In one of our patients, persistent glycosuria appeared whenever the blood-sugar rose to a level of 0.11 per cent.; at no time was there much glycosuria, and he always reacted to starvation; 27 grams of carbohydrate per day would induce a glycosuria which was not increased with an intake up to 50 grams.

Before meals his blood-sugar was 0.08 to 0.09 per cent., while after a mixed meal his blood-sugar rose to 0.11, or 0.12 per cent. with slightly glycosuria (see Chart V).

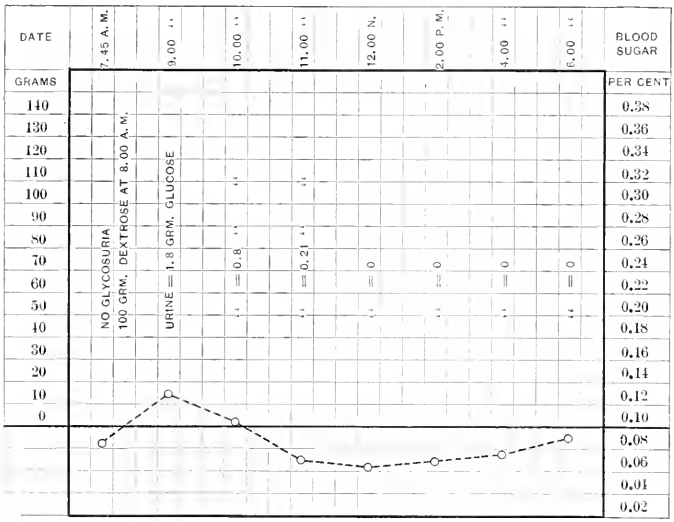

Chart V.

As a result of recent work, no doubt, the more frequent estimations of blood-sugar will demonstrate that renal diabetes so-called is less rare than has hitherto been believed.

Test Diet. In some cases a patient's tolerance seems to alter in a very short time, and appreciation of this is of the greatest importance in the use of test diets. Thus, for example, in one individual who had had a fat protein diet for three days, preceded by a low CHO intake for one week, there was a D : N ratio of 2.77 per cent., showing an inability to burn 43 per cent. of protein carbohydrates. He continued on a fat protein diet for twenty-one days, and during the first fourteen days the D : N ratio varied markedly, finally dropping to zero on the sixteenth day. On this day he burned 36 grams of protein CHO as well as 2 grams of CHO in 100 grams of chicken (*i. e.*, 38 grams CHO).

Reading the variations according to the Lusk-Falta formula we found the following:

$$\frac{35.9 \times 100}{12.97 \times 3.65 + 0} = 75.6 \qquad \text{13 days later,} \quad \frac{3.08 \times 100}{9.32 \times 3.65 + 2} = 8.5$$

Acidosis. Two important points are worthy of note in our observations:

1. The ferric chloride reaction is sometimes absent when acidosis is present, and is less sensitive, too, than the nitro-prusside reaction. 2. The urine does not always show a reaction for acidosis even when the blood gives a positive quantitative result. This latter is important as reminding us that the excretion of the acid bodies is not necessarily an index of the degree of acidosis.

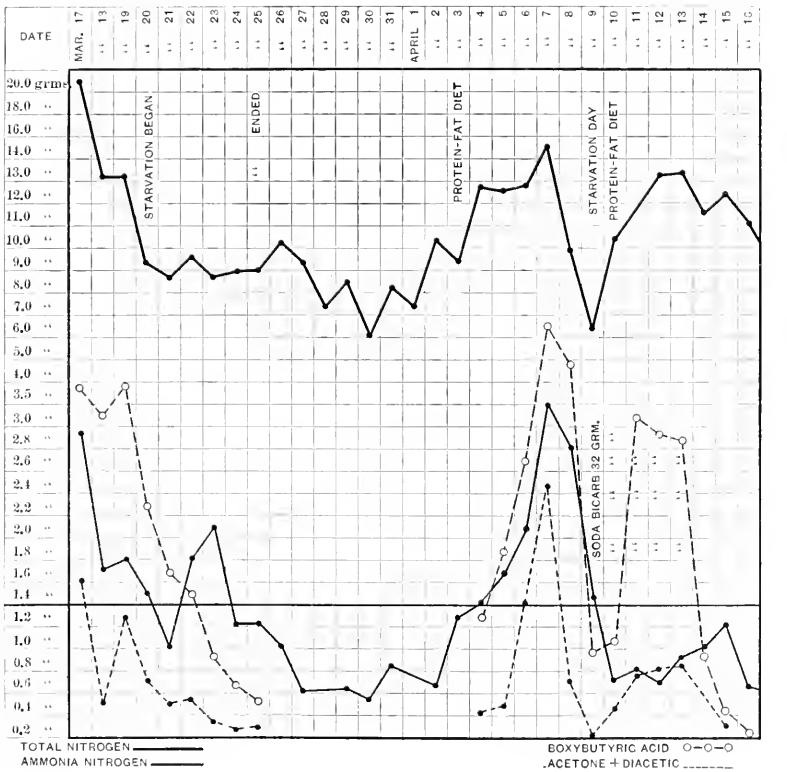

Chart VI.

Starvation in the ordinary individual usually results in acidosis, while in diabetes the reverse occurs. Allen, indeed, lays stress on this feature, and insists on the need of eliminating ketone bodies from the blood by means of starvation.

Sometimes, however, in our cases, acidosis was initiated by the starvation, at other times a preëxisting acidosis was increased, though usually it disappeared. Evidently there is a variation due to many circumstances, though starvation ultimately does make the urine acid-free.

In one persistent case of very mild diabetes, with prolonged mild acidosis, interrupted periods of a fat-free diet seemed especially useful in clearing up remnants of the acidosis.

In one very severe case in which the acidosis disappeared on starvation, it developed again on a protein fat diet, and later on disappeared with one day of starvation. Sodium bicarbonate was given (32 grams per diem) for five days, with resulting elimination of more ketone bodies. Excretion of these bodies ceased again with cessation of bicarbonate administration (see Chart VI).

Another experience worthy of note is the varying ratio of the acetone bodies to β-oxybutyric acid. Sometimes there is much acetone and little β-oxybutyric acid, and sometimes the reverse occurs. There seems to be little constancy, and the percentage of 60 to 80, as usually recorded is subject to many wide exceptions.

THE INFLUENCE OF ACIDOSIS ON HYPERGLYCEMIA IN DIABETES MELLITUS.

By Albert A. Epstein, M.D.,[1]

and

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new york city.

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Total fasting or the prolonged withdrawal of carbohydrates from the dietary of a normal or diabetic individual leads to the production of an acidosis. This is usually explained on the following grounds: (1) fats are oxidized secondarily through the combustion of carbohydrates:[2] (2) because of the withdrawal of carbohydrates (and also with the limitation of proteins) more fat than usual is called upon to supply the body energy. The resulting increased mobilization of fats associated with their incomplete combustion leads to the production of acid bodies. An increased protein metabolism (occurring synchronously) may add to or augment the production of similar substances.

[1] Work done under the tenure of the Moses Heineman Fellowship in Pathology.

[2] Naunyn: Der Diabetes Mellitus, 1906, p. 221.

The general effect of the overproduction of such bodies upon the organism is the coupling-up of all available alkalies. This in turn leads to a reduction of the amount of fixed alkali and ammonia in the body, a condition which constitutes an acidosis.

The acidosis may manifest itself in the following ways: (1) increased acidity of the urine, so that very large amounts of alkali are required to render it alkaline; (2) increased hydrogen-ion concentration of the blood serum; (3) diminished combining power of the serum for carbon dioxide, and hence (4) reduced carbon dioxide tension in the alveolar air; (5) increased ammonia output in the urine, combined with elimination of ketone bodies.

In addition to the other effects of acidosis on the body it has been shown by a number of investigators that it is in itself capable of inducing a glycosuria (so-called "Säure-Diabetes"). Elias[3] has demonstrated that the production of an artificial acidosis leads to a marked mobilization of glycogen from the liver and other depots. So too Pavy,[4] Kulz,[5] and Goltz[6] have shown experimentally that the intravenous and intrastomachal administration of various acids leads to a glycosuria. Numerous clinical observations of cases of acid poisoning have confirmed these findings. Moreover, Ruschhaupt[7] found that even the administration of acetone can cause a glycosuria. On the other hand, Murlin and Kramer[8] have shown that after the removal of the pancreas the introduction of sodium carbonate into the blood stream causes a diminution in the excretion of sugar. Even the respiratory quotient is increased in depancreatized animals after the administration of alkali.[9] In a recent communication, Underhill[10] shows that the control of acidosis (by means of alkali) is followed by the reduction of the glycosuria in a diabetic.

The intermediate step between a glycogen mobilization (due to acidosis) and glycosuria is an increase in the blood sugar. Another factor which may influence the degree of hyperglycemia is the function of the kidneys. Epstein and Baehr[11] have shown that in depancreatized animals, with impaired or abolished kidney function, the liberated sugar accumulates in the blood, causing very marked hyperglycemia. The impairment of renal function in these experiments is attributed to the acidosis. The effect of acidosis upon the blood-sugar may thus be twofold: (1) through its effect on the liver and muscles, causing a mobilization of glycogen, and (2) by interference with renal elimination of sugar, leading to its accumulation in the blood.

[3] Biochem. Ztschr., 1913, vii, 331.
[4] Naunyn, loc cit., p. 40.
[5] Pflüger's Arch., 1881, xxiv, 97.
[6] Centralbl. f. d. med. Wissensch., 1867, v, 705.
[7] Arch. f. exp. Path. u. Pharm., 1900, xliv, 126.
[8] Jour. Biol. Chem., 1913, xv, 365.
[9] Cited from F. P. Underhill: Tr. Soc. Exp. Biol. and Med., 1916, xiii, 111.
[10] Tr. Soc. Exp. Biol. and Med., 1916, xiii, 111.
[11] Jour. Biol. Chem., 1916, xxiv, 1.

The introduction of prolonged fasting as a means of treating diabetes has revealed the fact that not only does the glycosuria frequently disappear, but also that the acidosis clears up as well. However, observation of a large series of cases under such treatment has shown that whereas certain cases lose their glycosuria, hyperglycemia, and acidosis, certain others develop an acidosis or exhibit a very marked increase thereof. If not immediately controlled such cases prove to be rapidly fatal. On this basis, cases of diabetes may be divided into two groups: those in which fasting controls the hyperglycemia and causes the disappearance of symptoms, and those in which the withdrawal of food (particularly of carbohydrates) causes or aggravates the acidosis, thus rendering the diabetic condition much worse.

The studies which we have made show the effect of acidosis on carbohydrate metabolism, especially in cases that are unfavorable for starvation treatment, in which a vicious cycle is established by the withdrawal of food, and more particularly of carbohydrates. It has been frequently shown (Minkowski, Magnus Levy, Joslin and others) that even in very "severe" diabetes the body has the power to oxidize carbohydrates, and that carbohydrates are specific in reducing acidosis even when the ability of the body to burn them is very low. This beneficial influence of carbohydrates on the acidosis, and subsequently on hyperglycemia and glycosuria, is demonstrated in our studies.

The following cases are supplied as examples to illustrate the above observations:

Case I.—*Coma diabeticum, unusual hyperglycemia, associated with acidosis, in the terminal stage of the disease.*

W. S.; tailor; Austrian, aged fifty-seven years. Admitted March 22, 1916; died March 25, 1916. Chief complaints: polyuria and polydipsia for three weeks and repeated vomiting for four days. Physical examination revealed a tendency to stupor, deep inspirations, and acetone odor to the breath. On March 22 the patient was placed upon milk, 1500 c.c. per day, 5 per cent. vegetables ad. lib., Murphy infusion of 3 per cent. sodium bicarbonate (1000 c.c.) b. i. d., sodium bicarbonate by mouth, one dram, q. 2 h. The patient started to vomit and continued to expel all food and medication. Drowsiness and heavy snoring respiration became prominent. Three intravenous injections of alkali were given, but drowsiness soon merged into deep coma, and on the fourth day death intervened. All urinary examinations showed sugar, marked acetone, and diacetic acid (see Chart I).

Comment. Note the antemortem rise in blood-sugar (as shown in the diagram) to the unusual figure of 1 per cent. and concomitant fall in alveolar carbon dioxide. The urine was very small in amount during the entire period of observation. Some urine was lost because of involuntary micturition.

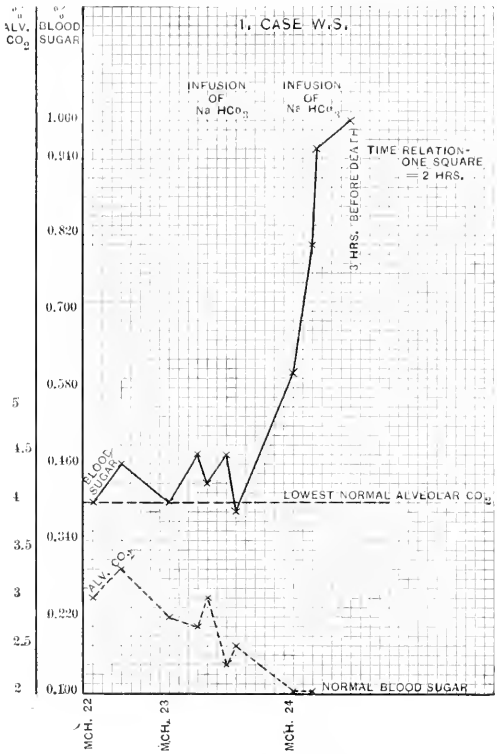

CHART I.—Case W. S.

CASE II.—*Coma diabeticum and abscess on the back.*

B. F.; aged forty-nine years. Admitted March 10, 1916; died March 17, 1916. Chief complaint: abscess on back, of two weeks' duration, and steadily increasing in size. The patient has had diabetes for nine years. Physical examination and subsequent operative procedure (on the day of admission) revealed an irregular red elevated fluctuating area in the interscapular region, discharging pus through a small sinus. Upon incision there was found an extensive cellulitis of the back, involving all of the deep tissues, and studded with necrotic material and abscess cavities. The patient was placed upon sodium bicarbonate, 1 dram every three hours, Murphy infusion of 3 per cent. sodium bicarbonate (1000 c.c.) b. i. d., whisky $\frac{1}{2}$ ounce, q. 2 h., 1500 c.c. of milk per day, and infusion of digitalis, $\frac{1}{2}$ ounce, t. i. d. The wound continued to drain profusely and the patient voided large amounts of urine (the average daily output being 3500 c.c.). On March 12 whisky was stopped and the carbohydrate was gradually increased in the form of 5 per cent. vegetables, until the patient, on March 15, was receiving 500 grams of 5 per cent. vegetables and 1 pint of skimmed milk. On March 16,

however, the patient started to vomit, the urinary output fell to 1990 c.c., drowsiness became more and more evident, and death ensued. All urinary examinations showed sugar, marked acetone, and diacetic acid (see Chart II).

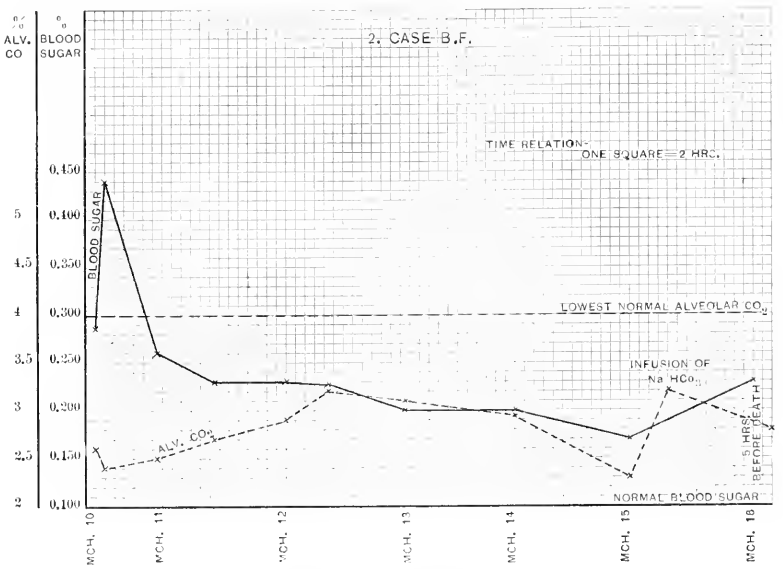

Chart II.—Case B. F.

Comment. This case demonstrates the effect of administration of carbohydrate and alkali on the acidosis. Associated with the reduction in the acidosis is a marked decrease in the hyperglycemia. The fall in the blood-sugar was accompanied by a reduction in the glycosuria. Just before death, however, as the urinary output diminished in amount, the alveolar carbon dioxide fell and the blood-sugar rose.

Case III.—*Coma diabeticum following the withdrawal of food.*

E. C.; operator; aged twenty-four years. Admitted February 15, 1916; died February 25, 1916. Chief complaints: pruritus vulvæ and nocturia for three months. Physical examination revealed an acetone odor to the breath and a severe dermatitis of the thighs and vulva.

Treatment. On February 15 and 16 strict antidiabetic diet (30 grams of carbohydrate); February 17 and 18 Allen régime of whisky and water; February 19, 30 grams of 5 per cent. vegetables allowed. On the following day the patient started to vomit the whisky, then all food and medication. Murphy infusions of 3 per cent. sodium bicarbonate were then started and the diet changed to skimmed milk, 1 quart per day. Vomiting continued, and on February 23 the

patient was becoming stuporous. Carbohydrate and alkali were given liberally (by rectum, per os, and intravenously), but the patient lapsed gradually into coma and died. The urinary examination showed sugar, marked acetone, and diacetic acid (see Chart III).

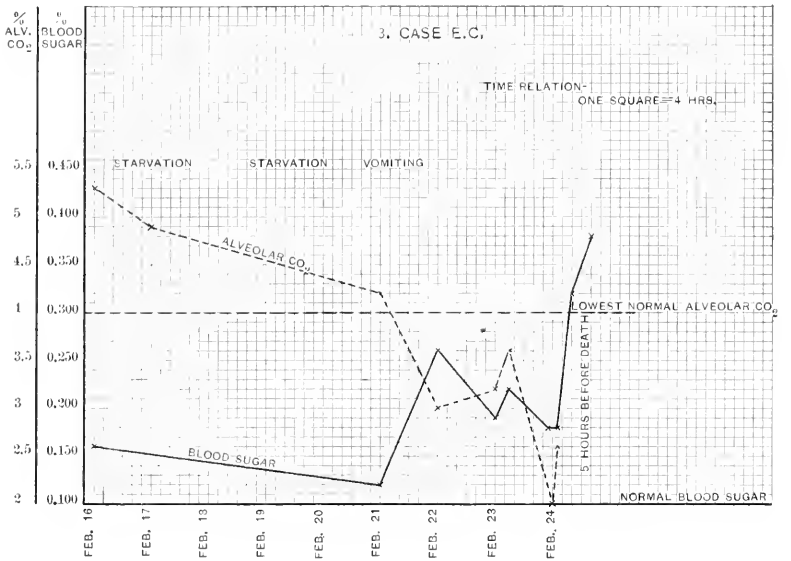

CHART III.—Case E. C.

COMMENT. The first effect of the withdrawal of food was a fall in the blood-sugar followed by a disappearance of the glycosuria. Associated with this apparently beneficial result there was a fall in the alveolar carbon dioxide and hence an increased acidosis, at first very gradual, then more rapid. As the acidosis developed the blood-sugar rose again and continued to rise.

The persistent vomiting rendered the condition uncontrollable.

CASE IV.—*Diabetic acidosis and hyperglycemia, induced by restricted diet, relieved by the liberal administration of carbohydrate.*

G. M.; housewife; Russian; aged twenty-four years, pregnant six weeks. Admitted January 21, 1916; discharged February 24, 1916. Chief complaints: polydypsia, polyuria, loss in weight for nine months. Has been on a diet all this time, and has had several fasting days. Normal weight, 146 pounds; present weight, 110 pounds. Physical examination revealed an acetone odor to the breath, emaciation, and dry skin. On January 21 the diet consisted of skimmed milk, 1 quart per day, 500 grams of 5 per cent. vegetables, whisky 2 ounces, black coffee, and chicken broth. This diet contained approximately 70 grams of carbohydrate. Upon subse-

quent days the carbohydrate allowance (mainly in the form of 5 per cent. vegetables and skimmed milk) was from January 22 to January 24, 30 grams of carbohydrate; January 24 to February 18, 32 grams; February 19 to February 22, starvation (see Chart IV).

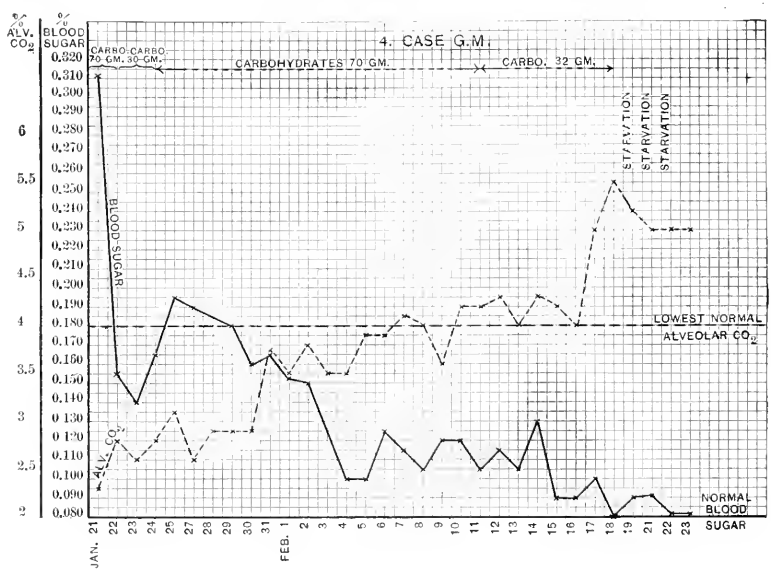

Chart IV.—Case G. M.

Comment. It is evident that this case was benefited by the liberal allowance of carbohydrate, the blood-sugar on the first day falling from 0.312 per cent. to 0.140 per cent., although the patient was receiving 70 grams of carbohydrates daily. The blood-sugar continued to fall gradually, while the alveolar carbon dioxide progressively rose. The urine was large in amount, and while on admission it showed the presence of sugar, much acetone, and diacetic acid it gradually cleared up. On February 6 the diacetic acid had disappeared, and on February 17, there was only a trace of acetone. The urine became sugar free on February 18, when the blood-sugar also fell to normal.

Summary. The observations made in this study point to the following conclusions:

1. The withdrawal of food from certain cases of diabetes provokes, or aggravates the acidosis.

2. The acidosis causes an increase in the blood sugar content, in one of two ways: (*a*) by augmenting the mobilization of sugar (Case IV), and (*b*) by affecting the sugar-secreting function of the kidneys (Case I).

3. Liberal, but judicious, administration of carbohydrate may control the acidosis provoked by the withdrawal of carbohydrates

or complete fasting, thus leading to a general amelioration of the diabetes (Case IV).

4. A progressive rise in the blood-sugar content, associated with a gradual fall in the alveolar carbon dioxide is indicative of impending coma (Cases I and III).

We wish to acknowledge our indebtedness to the attending physicians of the hospital for the privilege of observing some of their cases.

A FATAL CASE OF DIABETES MELLITUS ASSOCIATED WITH LARGE-CELL HYPERPLASIA.

By John R. Williams, M.D.,
ROCHESTER, N. Y.,
AND
M. Dresbach, M.D.,
ITHACA, N. Y.

(From the Department of Physiology, Cornell Medical College, Ithaca, N. Y.)

The following case[1] is reported chiefly because the association of diabetes mellitus with large-cell hyperplasia has rarely been recorded. Moreover, certain histological changes to be described in this paper are believed to be an expression of a disturbance of fat metabolism, recent study of which has yielded important facts bearing, (1) upon the origin of fat under certain conditions in the spleen, liver, adrenals, lymph nodes, and bone marrow, and (2) upon the treatment of diabetes. Furthermore, the large-cell hyperplasia here described bears a certain superficial resemblance to the cellular changes in the spleen in that interesting and comparatively rare condition known as primary splenomegaly Gaucher, or Gaucher's disease, which has been believed by some, on insufficient grounds, to be a disturbance of fat metabolism.

There has been a great deal of confusion in the literature on this disease since it was first announced by Gaucher[2] in 1882, and a considerable number of mistaken diagnoses have been made. The following report may help to emphasize the importance of making

[1] Under the title "The Possible Association of Diabetes Mellitus and Splenohepatomegaly Gaucher," we gave a preliminary report of this case in the Proceedings of the Society for Experimental Biology and Medicine, New York, November 17, 1915. As some others have done, we depended mainly upon the histological examination of the tissues—spleen, liver, and lymph glands—in making our decision, though we recognized that the clinical history of the case did not support us. We take this opportunity to present the facts which establish the correct diagnosis. The case presents some unique points as far as the pathology in diabetes is concerned. As far as we can learn they have not been reported before in this country.

[2] De l'epithelioma primitif de la rate, Paris, 1882.

careful histological, polariscopic, and microchemical tests when it comes to deciding whether or not the pathology of a given spleen is that of true Gaucher's disease. (See the papers by Brill and Mandlebaum[3] and Mandlebaum and Downey.[4 5]

CASE NOTES.—S. R. J., male; white; American; aged twenty-eight years; single; civil engineer. Patient complains of weakness, excessive thirst, and frequent and copious urination, insomnia, and constipation.

In the spring of 1911 patient first noticed that he had excessive thirst and frequent urination. In the summer of 1911 sugar was found in his urine.

Previous Illness. During the preceding four years he had been working out of doors at his profession, engineering, chiefly field and irrigation work. Had enjoyed unusual health. In the year 1910 patient was struck by timber on right shoulder. This caused a slight injury, which produced a lameness lasting only for a day or two. In the year 1907 patient had a diseased lymphatic gland removed from the left inguinal region. This is thought to have been caused by an infection in the foot.

As a child the patient had slight attacks of scarlet fever, measles, and mumps, from which he made good recoveries. No history of nervous or venereal disease.

Family History. Father living at sixty-four years of age; well. Mother living at sixty-two years of age; well. Patient has two brothers, living and well. No history of diabetes among the immediate or collateral relatives.

Weight. Best weight, 145 pounds, 1909. Spring, 1912, 136 pounds. July 5, 1912, 134 pounds.

Physical Examination, July 5, 1912. Medium height. Fairly well developed. Thin panniculus. Teeth: many filled. Marked pyorrhea of molars. Tongue swollen and teeth-marked. Lungs clear; no areas of dulness; no rales. Heart normal in size and position. No bruit. Reduplication of second sound at apex on the tenth to twentieth beat. Rate in upright position, 108 per minute; horizontal, 80 per minute. Systolic blood-pressure, 110 mm. Nothing abnormal noted in the abdomen.

BLOOD EXAMINATIONS.

July 6, 1912. Total leukocytes, 6,040. Red cells, 5,420,000. Differential leukocyte count:

Large lymphocytes	4.0 per cent.
Small lymphocytes	19.0 "
Transitionals	3.0 "
Polynuclear neutrophiles	72.0 "
Polynuclear basophiles	1.0 "

[3] Folia Hematologica, 1916.
[4] JOUR. AM. MED. SC., 1913, cxlvi, 863.
[5] Johns Hopkins Hosp. Bull., 1916, xxvii, 302.

October 9, 1912. Differential count:

Large lymphocytes	7.1 per cent.
Small lymphocytes	9.8 "
Transitionals	5.3 "
Polynuclear neutrophiles	73.6 "
Polynuclear eosinophiles	1.3 "
Polynuclear basophiles	0.9 "
Large broken-down white cells	1.7 "

July 17, 1913. Differential count:

Large lymphocytes	13.4 per cent.
Small lymphocytes	1.8 "
Transitionals	1.2 "
Polynuclear neutrophiles	78.0 "
Polynuclear eosinophiles	3.6 "
Normoblasts	14.0 "

Early in the illness (September, 1912) the patient was examined in consultation by Dr. Elliot P. Joslin, who also noted nothing abnormal in the patient's abdomen. Our attention was not directed to the spleen, however, and it is not improbable that a slight enlargement of it was overlooked.

Because of the prominence of the patient and of his family, many physicians in various parts of the United States were consulted in this case. Practically every known dietary and medical treatment was employed at the suggestion of these various clinicians. The patient resided in Ithaca; the general clinical supervision of the case and the urine examinations were conducted by one of us in Rochester.

In the year 1912, when this patient was under observation, clinicians generally believed that the most important factor in the problem of diabetes was carbohydrate metabolism. The significance of fat and protein metabolism and the total caloric needs of the diabetic were not clearly understood, and were given only minor consideration. It was generally believed that a patient with diabetes must, for the maintenance of life and comparative health, have a minimum food intake of at least 30 calories per kilo of body weight. On this basis the patient, weighing approximately 134 pounds or 61 kilos, would have required daily at least 1830 calories while at rest and at least 15 per cent. more, or approximately 2200 calories, while undergoing moderate exercise.

The clinical experience of one of us (Williams) during the past year, in which more than 50 cases have been accurately studied with reference to this point as result of the epoch-making work of Allen in the Rockefeller Institute, demonstrates that patients can live in comparatively good health on total food intakes far below these minimum standards which had hitherto been thought necessary.

Furthermore, recent clinical experience has shown that the feeding of the average diabetic beyond this formerly supposed normal minimum requirement of 30 calories per kilo of body weight will

TABLE I.—SHOWING URINE EXAMINATION AND FOOD INTAKE ON VARIOUS DAYS THROUGHOUT TREATMENT.

Date.	Urine.					Diet.				
	Volume.	Specific gravity.	Diacetic acid.	Total NH_3 (Folin).	Sugar (polar).	Carbohydrate.	Protein.	Fat.	Alcohol.	Calories.
1912										
July 5	1200	1023	++	1.9	48	20	100	200	0	2310
6	960	1026	++	2.1	27	65	100	200	0	2500
27	2490	1023	+	0.6	30	90	33	74	0	905
Aug. 8	2660	1030	++	2.7	86	190	75	200	0	3000+
Oct. 20	2040	1031	+	0.6	45	64	75	30	12	1010
31	2460	1026	0	0.3	38	45	75	30	12	949
Nov. 12	2160	1025	0	0.5	56	56	75	30	12	878
1913										
Jan. 28	4080	1031	+++	2.6	122	35	100	200	0	2370
Feb. 2	3630	1033	+++	3.0	152	66	90	200	0	2450
June 12	3600	1030	++++	4.1	108	90	100	200	0	2640
July 27	3630	1030	++++	4.4	123	200	150	180+	0	3000
31	3930	1027	++++	3.3	172	200	150	180+	0	3000

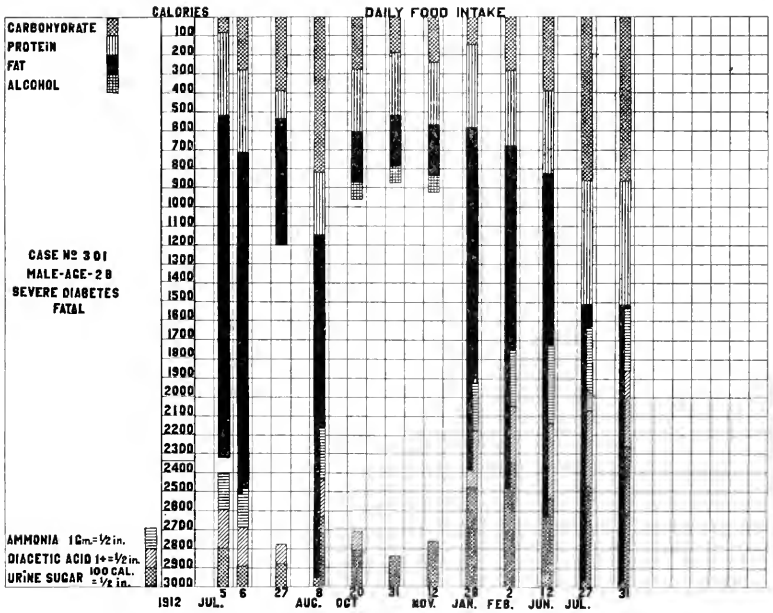

CHART I. Plotted from Table I.—Showing graphically the relation between the food intake and urine outgo. Food intake for each day reads from above down in calories. The urine examinations read from the bottom up as shown by key at end of chart. It will be noted that on days when much food was fed, particularly fat, the acidosis as measured by the ammonia and diacetic acid excretion was worse. On August 8 the patient was given an oatmeal diet. The various diets shown in this chart represent the culminations of various dietary procedures.

precipitate in the majority of cases of advanced diabetes both glycosuria and acidosis; and if, as was formerly taught, the patient be fed much in excess of this so-called standard, not only will his tolerance for carbohydrate be seriously impaired but his acidosis will be proportionately increased. This fact is illustrated by Table I and Chart I.

In a study of this table it will be observed that on those days when the patient was fed a diet low in fat the severity of his acidosis, as measured by the ammonia output, declined. It is altogether probable that had this dietary procedure been pursued further the diabetic condition would have been ameliorated, for when it was thought desirable to restore the losing weight of the patient and apparent weakness by feeding the patient large amounts of fat his acidosis increased in severity. This is the justification for the belief, from a clinical stand-point, that the patient had a serious failure in fat metabolism.

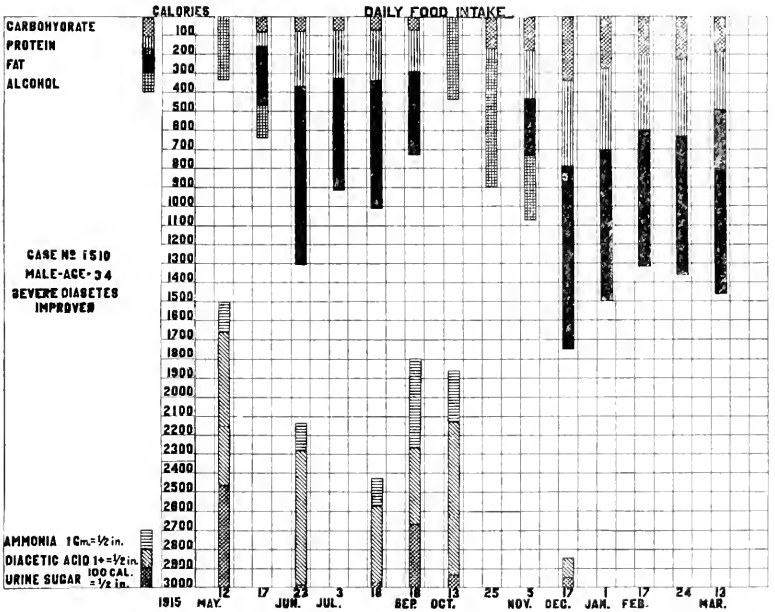

CHART II.—Illustrates present method of treating diabetes. Compare with Chart I. Severe diabetes and lipoidemia in a young male. Case similar in many respects to the one described in this paper. This patient had a marked acidosis and very low tolerance for food. There was almost complete intolerance for fat. By feeding the patient on fat-free and low-fat diets his condition has been much improved, although the cholesterol content of the blood remains high. The data above shown are from test days after periods of such treatment. Food intake reads from above down in calories, the different food principles being represented by the different cross-hatchings as shown in the key. The urine outgo reads from the bottom up; urine sugar plotted in calories; diacetic acid and ammonia are shown in the key.

Because of this erroneous belief about the normal minimum food requirement, and because of the then current clinical teaching, in effect that fat should constitute the major portion of a diabetic's diet, this patient was fed fat in considerable amounts, as indicated in Table I and Chart I.

To contrast the effects of high and low fat content in the diet in severe diabetes we insert a graphic record (Chart II) of a case now under treatment. Table II gives dietetic and other details. It will be observed that the cholesterol content of this patient's blood has been very high. The presence of this substance in the tissues and certain of its experimental effects will be discussed later.

TABLE II.

Blood removed.	Diet previous twenty-four hours.				Urine sugar.	Free ammonia.	CO_2 in lung air, mm.	Cholesterol per 100 c.c. blood, mg.
	Carbohydrate.	Protein.	Fat.	Calories.				
1916								
Mar. 14	44	69	108	1428	0	0	36.2	510[6]
April 10	43	71	88	1258	40	0.82	41.2	428
May 11	33	84	96	1363	..	..	30.0	833
15	61	35	21	674	101	2.81	31.4	717
23	No food 15 hours previous				19	1.21	39.3	833

Returning to the case under discussion, we may say that there was nothing unusual in the general course of the disease. It progressed steadily and the patient died in coma August 1, 1913.

Postmortem Examination. Body was embalmed one hour after death. The fluid used contained about 7 per cent. of formalin and a small amount of carbolic acid. Postmortem was held twelve hours after death, the object at the time being mainly to secure the pancreas. Abdominal organs only were examined.

Macroscopic findings: All organs had a normal appearance except the spleen, which was somewhat enlarged. It weighed 330 gms. Shape not unusual; dimensions: 13 x 10.5 x 6 cm. Color normal, both superficially and when sectioned. No amyloid areas.

Microscopic examination:[7] Pancreas, liver, spleen, kidneys, adrenals, and lymph glands were sectioned. Specimens were fixed in formalin, Zenker's fluid, and osmic acid.

Kidneys normal.

Pancreas: No generalized increase in connective tissue, but some

[6] Cholesterol estimation was made by Prof. W. R. Bloor, whose method (Jour. Biol. Chem., 1916, xxiv, 227) is employed in the tests. Normal blood contains between 170 and 240 mg. cholesterol per 100 c.c.

[7] Specimens of the spleen and pancreas were examined by Drs. L. Hektoen, James T. Ewing, E. L. Opie, and A. S. Warthin, to whom we desire to express our thanks for valuable reports and suggestions.

indication of atrophy, with duct stasis. Few areas of strongly acidophile alveoli. Islets normal in number and distribution. Some islets enlarged, in few instances to twice ordinary size. No marked abnormality of structure shown, but there was a tendency to hypertrophy and to contain hyperchromatic nuclei. Islet cells closely packed together, and difficult to distinguish, with cell masses separated by conspicuous capillaries, walls of which appeared somewhat thickened. Slight sclerosis. No evidence of hyaline change in islet epithelium (see Fig. 1).

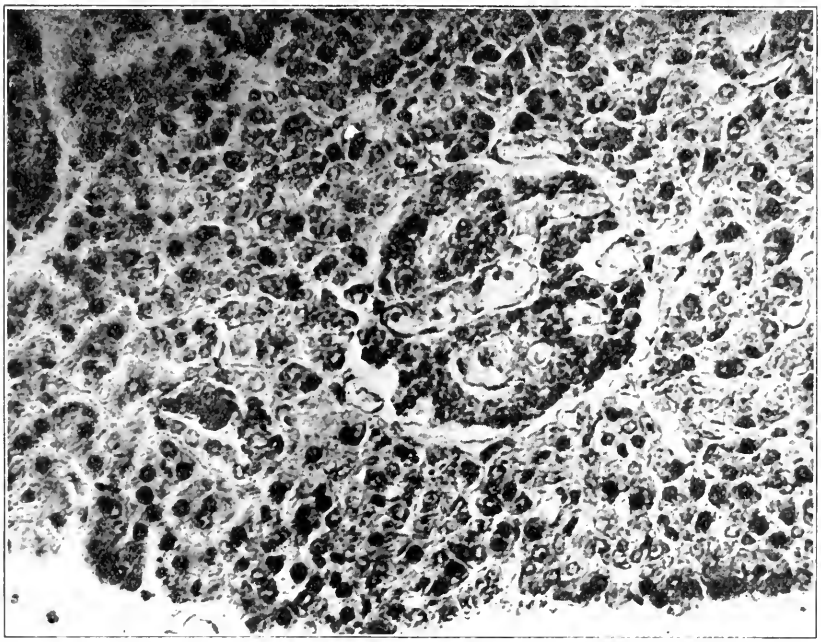

FIG. 1.—Section of the pancreas, showing a single islet. Zenker fixation. Iron hematoxylin. × 400.

Spleen: The spleen throughout contained numerous large cells. These cells were mostly round or oval, and were of varied size. They were especially abundant in the pulp, but some could be seen to penetrate into the periphery of the nodules. Nodules otherwise were normal. Scarcely any sclerosis. No giant cells noted. Further description given below (see Fig. 2).

Lymph glands: Two lymph glands from the duodenal mesentery were sectioned. They showed the same large cells as did the spleen, though the cells were smaller and not so plentiful as in the spleen. No pigment was present (see Fig. 3).

Liver: A few cells bearing superficial resemblance to those in the spleen were found in the liver sinusoids; not more than three or

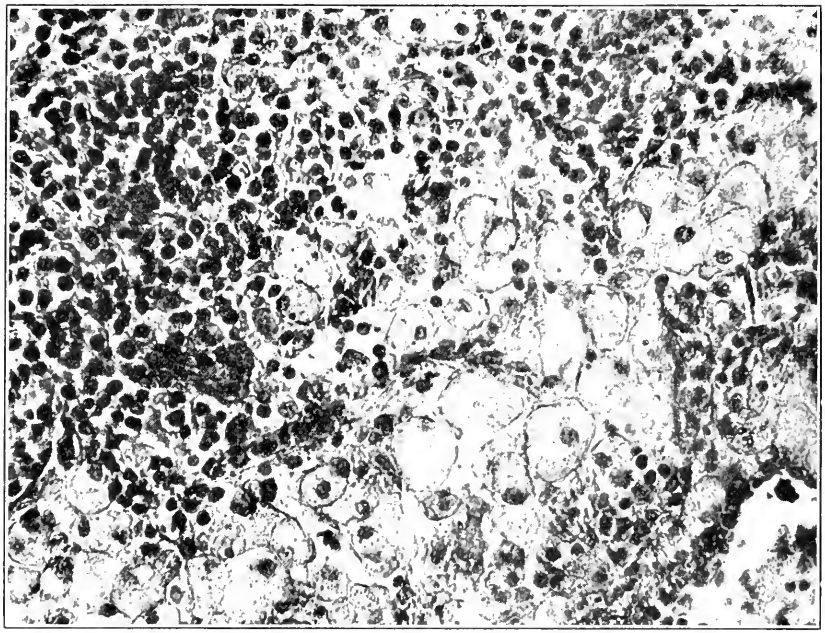

FIG. 2.—Section of the spleen, showing large-cell hyperplasia. Zenker. Hematoxylin and eosin. × ca. 350.

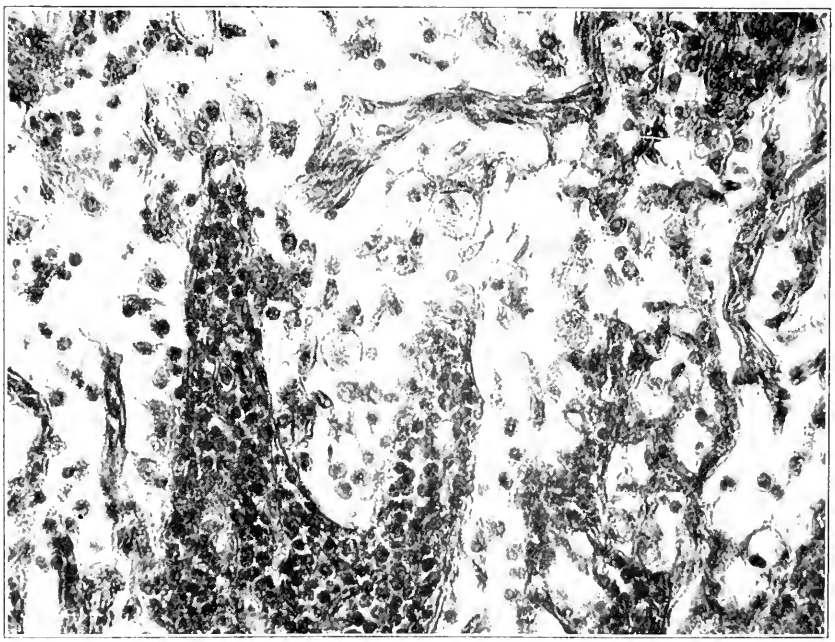

FIG. 3.—Section of a mesenteric lymph gland. A few large hyperplasia cells are seen about the middle of the section. Zenker. Hematoxylin and eosin. × ca. 350.

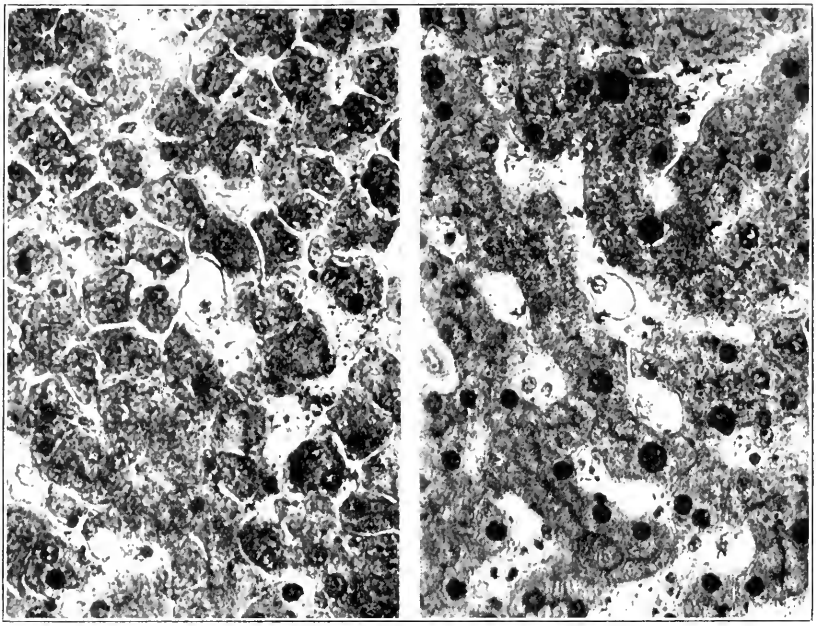

FIG. 4.—Two sections of liver. In the middle of each section may be seen a single Kupfer cell, located in a sinusoid. See text for description. Formalin. Iron-hematoxylin. × 350.

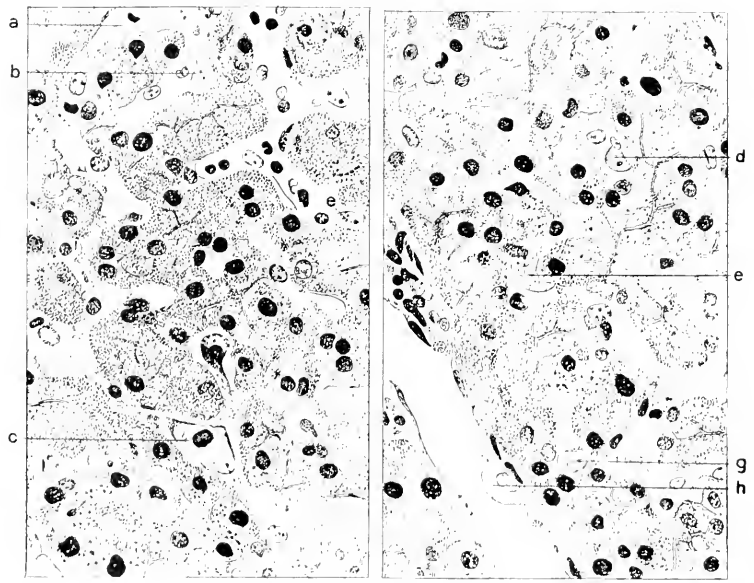

FIG. 5.—Microprojection drawing of two liver sections. Kupfer cells are seen at *a*, *b*, *c*, *d*, *e*. At *a* large cell which apparently has wandered into a vein is marked. × 400.

four generally were seen in a lobule, though occasionally they were fairly numerous (see Figs. 4 and 5).

Further details about the liver and adrenal glands are given in the following comments, which were made, in a personal communication to the authors, by Dr. Frank S. Mandlebaum,[8] who kindly examined the tissues:

"It cannot be denied that the large cells in the spleen have a certain resemblance to the large cells of Gaucher's disease, but pictures of this kind are found in a variety of pathological processes. The cells in your cases are more rounded in outline than those of Gaucher's disease, the characteristic wrinkled and streaked appearance of the cytoplasm is missing, and the impression is obtained that some substance originally contained in the cells has been dissolved out in the process of hardening and embedding. Furthermore, dilated venous sinuses filled with blood and large cells are not prominent. The sections of the liver do not in any way resemble those of Gaucher's disease, even though some large cells are present in the sinusoids. The lesion is a granular degeneration with hypertrophy of the stellate cells of Kupfer (see Figs. 4 and 5), with secondary proliferation and desquamation. Some of these cells may have been carried to the liver from the spleen through the portal circulation. The lesion in the lymph node is a marked hyperplasia of the cellular reticulum such as is frequently found in many pathological processes, but bears no resemblance whatever to the lesion of Gaucher's disease.

"Examination of the blocks of tissue of the spleen and liver reveal the true nature of the pathological process. Fortunately the tissues were fixed and preserved in formalin, therefore the substance in the large cells can be identified. Frozen sections of the spleen stained with Sudan III and Nile blue show the presence in the large cells of a considerable amount of neutral fat and lipoids. The polariscope shows anisotropic bodies which disappear on heating and reappear on cooling, thus proving the presence of cholesterin esters. Polariscopic examination of liver sections stained with Nile blue shows that the cholesterin esters are present in the stellate cells of Kupfer. Unfortunately no material from the lymph nodes is available. therefore lipoid tests cannot be made. I feel, however, that the large swollen reticular cells in the lymph nodes would show the same microchemical and polariscopic reactions.

"Although the histological picture in your case is sufficient proof that this is not an instance of Gaucher's disease, the simple presence of fat and lipoids in the large cells is positive evidence that the case does not belong to this group, for these substances have never been found in any of the authentic cases. I might also say that the clinical history of the case, as published in your preliminary

[8] This case is the one referred to by Drs. Mandlebaum and Downey in their paper in the Johns Hopkins Hosp. Bull., April, 1916, vol. xxvii, No. 302.

report, together with the autopsy findings, are not suggestive of Gaucher's disease.

"I have no hesitancy, therefore, in stating that your case is one of lipoid deposits in the spleen and other organs, due to diabetes with a probable lipoidemia."

In a later letter Dr. Mandlebaum wrote to us concerning the adrenals as follows:

"Polariscopic examination of frozen unstained sections of the adrenal shows an appreciable increase of double refracting substances, especially confined to the zona glomerulosa and zona reticulosa, with some infiltration of the zona fasciculata as well. These substances disappear on heating and reappear on cooling. When frozen sections are stained with Nile blue a confirmation of the above findings is obtained. With Sudan III the cells of the zona glomerulosa are filled with bright yellow droplets. The cells of the zona fasciculosa appear enlarged, with the yellow droplets at the periphery of the cells and in the cells in the walls of the capillaries. The cells of the zona reticulosa are more completely filled with these droplets. Several small islands of cortical cells are found in the medullary portion of the gland, giving typical reactions with Nile blue and Sudan III.

"Treating sections of the adrenal with alcohol causes a complete disappearance of the anisotropic bodies, and upon subsequent staining with Nile blue and Sudan III no reactions for lipoids are obtained.

"Paraffin sections stained with hematoxylin and with Van Gieson show hypertrophy of the cells of the zona glomerulosa. These cells are increased in number and in size, and some have undergone granular degeneration. The hypertrophy of the cells is even more marked in the zona fasciculata and corresponds to the lipoid infiltration produced experimentally in rabbits and guinea-pigs by feeding with cholesterol (Antischow). The findings in the adrenal are still further proof of the probable lipoidemia in your case."

A fact worthy of note in this case is the absence of evidence of malfunctioning islets in the pancreas. Other instances of this sort are well known. On the other hand, degenerative changes in the islets have frequently been seen in diabetes, both in the human subject and in experimental animals. The amount of islet tissue necessary doubtless varies in different animals. In unpublished experiments by one of us in Ithaca with Dr. C. W. Webb, of Clifton Springs, N. Y., we have been astonished to see several dogs live a number of weeks with an extraordinary small amount of islet tissue. One dog had the head of the pancreas removed and the distal duct tied. He lived six months, free from glycosuria as long as he was given meat only, on which diet his weight decreased from 11 kg. to 5.5 kg. He developed distemper and was killed. We could find nothing but a strand of connective tissue one inch long repre-

senting the part of the pancreas left in the animal, and no islet cells could be identified.

Concerning the Lipoids. Lipoidemia has long been known to be present in diabetes (see Kusunoki[9] for index to literature), and there is reason to suspect that it occurs frequently in advanced or serious cases. One of us (Williams) in a recent, not yet reported, study of 22 cases of advanced diabetes found the cholesterin content of the blood increased in 16 cases. We find in the literature, however, very few cases of diabetes that resemble ours in histopathology. As Anitschow[10] says, it is very desirable that such cases be reported. The first instance of large-cell hyperplasia in this disease which we have found was given by Schultze,[11] who, according to Anitschow,[12] would be entitled to priority in the matter. Schultze regarded the large cells of the spleen in his case as probably identical with those in Gaucher's disease. In this he was doubtless mistaken, for, according to modern views (see Mandlebaum and Downey[13 14]), these large cells in Gaucher's disease contain no lipoids. They were present in Schultze's case in large amount, and there was marked lipoidemia.

Later, Lutz[15] described 2 cases of lipoidemia in diabetes with similar hyperplasia of the spleen. The cells contained isotropic fat, mostly, but there was some in the anisotropic form. Although Lutz notes the marked similarity of the microscopic picture in his cases with that in Gaucher's disease, he did not claim that the pathological processes were identical. In the cases of Schultze and Lutz the liver, adrenals, and bone marrow were not said to be involved, though the lymph nodules were found by Lutz to contain large cells infiltrated with fat. They appeared to be desquamated endothelial cells.

These facts are enhanced in interest and importance when taken in connection with the effects of hypercholesterolemia, as reported by Anitschow, Chalatow, Krylow, Rothschild, Sternberg, Landau and McNee, Soper in Ziegler's *Beitr. z. path. Anat. u. allg. Path.*, 1913 and 1914, and by Adler,[16] Bailey,[17] Borberg[18] and others. While we cannot give an analysis of the literature in this article, we may state briefly that it has been shown by feeding animals with cholesterin for several months that a hyperplasia, with lipoid infiltration, can be produced in the spleen and bone marrow. The spleen hyperplasia is strikingly similar to that seen in the case of

[9] Ziegler's Beitr. z. path. Anat. u. z. allg. Path., 1914, lix, 564.
[10] Ibid., 1913–1914, lvii, 201.
[11] Verhandl. d. deutsch. path. Gesellsch., Strassburg 15 Tagung, 1912.
[12] Loc. cit.
[13] Loc. cit.
[14] Loc. cit.
[15] Ziegler's Beiträge, 1914, lviii, 273.
[16] Jour. Exp. Med., 1914, vol. xx.
[17] Ibid., 1916, xxiii, 69.
[18] Skand. Arch. f. Physiol., 1914, xxxii, 287.

diabetes which we have described in this paper. (Presumably the bone marrow in our own case would have shown the same pathological feature, but unfortunately we did not take a sample of the marrow, as we had no suspicion of hyperplastic change at the time the tissues were fixed.) Other interesting results of these experiments, such as atheromatous conditions of the aorta, were obtained by Anitschow and others. For these details the reader is referred to the papers above cited.

On the chemical side numerous studies are available in the works of the several authors mentioned above. From these investigations one sees that the tendency is more and more not to regard the regulation of the lipoid supply of the body as the function of any one organ, as, for instance, the liver, which has received so much attention in former years. It appears that the spleen, adrenals, and bone marrow, as well as the liver, play an important part; whether jointly or separately is not yet clear. Aside from its digestive function the pancreas may also contribute in some way. Aschoff has become so convinced of the interrelation of these organs that he regards certain endothelial structures in the bone marrow, spleen, and lymph nodes, and the stellate cells of Kupfer in the liver, together with the adrenal cortex, as the "endothelial metabolism apparatus," the conception being that it, as well as other tissues of the body, is concerned with the intermediate metabolism of cholesterin (Landau[19]). English authors, *e. g.*, Dorie, Ellis, Fraser and Gardner,[20] believe that a "cholesterin balance can be maintained in the body by the food intake." Certain French writers (Chauffard and others) think that the adrenals secrete cholesterin (see Rothschild[21]). They stand practically alone in this view. (For recent discussion of the subject see Rothschild's papers[22]). Ciaccio[23] lays stress on the apparent relations of the lipoids, phosphatids, cholin, and glycerin esters. He thinks they have a complex history in the adrenals and other organs.

Another statement bearing on the question of fat metabolism may be made in this connection. In regard to the causes of fatty infiltration (and degeneration), Fischer and Hooker[24] make an attractive suggestion in a recent article on the physical chemistry of emulsions. They hold that an important factor in the stabilizing of an emulsion is the state of the colloid that may be the emulsifying agent. A fat emulsified in a hydrated colloid may be made to separate out by altering the hydration capacity of the colloid by acids, or, in some instances, by alkalies. Fischer and Hooker believe that fat in tissue

[19] Ziegler's Beiträge, 1914, lviii, 667.

[20] Proc. Roy. Soc. (Biology) London, 1908, pp. 212, 227; 1908, pp. 109, 129, 230, 505; 1910, p. 559; 1912, p. 461.

[21] Ziegler's Beiträge, 1914, lx, 39.

[22] Ziegler's Beiträge, 1914, vol. lx.

[23] Arch. f. exp. Pathol. u. Pharmacol., 1915, lxxviii, 347.

[24] Science, 1916, N. S., xliii, 468.

cells is thus emulsified, and that it may appear in visible form when the hydration capacity of the tissue colloids is decreased. Hence, according to this view, a fatty infiltration may have an entirely different cause from those ordinarily offered. Might not the acidosis of diabetes favor this phenomenon of the appearance of lipoids in the tissue cells and blood in this disease?

In conclusion, one sees there is a tendency on the part of not a few writers to build up a polyglandular theory of fat metabolism similar to that proposed by von Noorden and others to explain the control of the carbohydrates in the body. This theory regarding the carbohydrates and the origin of diabetes has been somewhat discredited by Minkowski, Opie, and Allen.[25] Nevertheless, a close correlation of organs by hormones or other bodies is a fundamental point in physiology, and one to be taken into account, along with other factors in considering any disorder of metabolism.

The whole question of fat metabolism is in need of much further study, which must not overlook the importance of the carbohydrates, for, as Bloor[26] states in a recent contribution to the subject of fat assimilation, sugar appears to be necessary in some stage for complete combustion in the oxidation of fats.

From studies, with the more refined technic of the present day, we may expect to see rapid progress toward a clear understanding of the etiology and pathology of diabetes.

SUMMARY. A case of fatal diabetes with large-cell hyperplasia of the spleen, lymph nodes, and liver is presented. It is the fourth case on record so far as the authors can tell. Other cases have doubtless occurred, but the hyperplasia has been overlooked. It is highly desirable, therefore, that thorough autopsies be made whenever possible. The spleen, lymph nodes, adrenals, liver, and bone marrow especially should be examined, microscopically and with the polariscope, to determine the nature of the cell contents.

The hyperplasia in the case described, and in the other cases reported, has some resemblance to the cell changes in Gaucher's disease of the spleen. In this disease lipoids are absent in the large cells, which, furthermore, have characteristic histological features. Moreover, Gaucher's disease is a familial disorder.

It is shown that overfeeding with fat increases acidosis in diabetes and probably bears some relation, as yet not understood, to lipoidemia. The acidosis is readily controlled, as Allen and Joslin have shown.

A brief discussion of some of the newer ideas regarding fat metabolism is given.

We wish to make acknowledgments to Professors B. F. Kingsbury and S. H. Gage for assistance with the photographs.

[25] Glycosuria and Diabetes, 1913, p. 842.
[26] Jour. Biol. Chem., 1916, xxiv, 447.

RENAL GLYCOSURIA.

By John R. Murlin, Ph.D.,

and

Walter L. Niles, M.D.,

(From the Physiological Laboratory of the Cornell University Medical College and the Second Medical Division of Bellevue Hospital, New York City.)

During the past summer the writers were engaged in a study of the influence of alkali, administered by duodenal tube, upon the glycosuria and hyperglycemia of human diabetes.[1] Among the cases which presented themselves was the following:

Case History.—Frank B., a poorly nourished young man, aged twenty years, was admitted to Bellevue Hospital on June 28, 1916. His family history was negative for tuberculosis and diabetes. He had had measles only as a child, and had always been strong and well up to the present illness, which began in November, 1914, with pains in his abdomen and epigastrium after meals. He also had furuncles, polyuria, and thirst, and became very weak in spite of a good appetite. He lost ten pounds in one month. He was then told by physicians that he had diabetes, and went to a hospital, where he was dieted, leaving the hospital sugar-free. Since that time he had been eating very little starch and no sugar. His urine was examined in October, 1915, and sugar was present. Since June 1, 1916, he had lost more weight and felt extremely tired. Upon admission to the hospital his thirst was not excessive, and he had no polyuria or infections.

His physical examination was negative, except that his tongue was slightly reddened and his breath gave a faint odor of acetone. The reflexes were a little sluggish.

On July 2 the patient was placed on a restricted diet containing 50 grams of carbohydrate, with a total food intake of about 35 calories per kilo. On the second day of this diet he excreted 24 grams of glucose. When the diet was changed (see table) so as to contain 15 grams of carbohydrate, he continued to excrete the same amount of sugar. By this time we had already suspected the nature of the glycosuria. Examination of the blood-sugar at 11 A.M., five hours after breakfast, revealed a normal percentage on several days. The diet was continued, with but slight variations, for eight days, and throughout this period the amount of sugar excreted did not vary more than 2 grams from a mean of about 26 grams daily, which was 11 grams more than the food contained. He was evidently also in minus nitrogen balance, for the urine alone contained some 4 to 6 grams more of nitrogen than did the food. Of this amount

[1] Murlin and Craver: Jour. Biol. Chem., December, 1916, vol, xxvii.

5 per cent. was ammonia nitrogen. The degree of acidosis, therefore, was mild.

When the carbohydrate in the food was increased to 100 grams, mainly by the addition of oatmeal, the excretion rose on the first day 10 grams, the next day 6 grams more, and then it returned in two days to about its former level. During the last four days of this period it fell 3 or 4 grams below this level. The blood taken at the same time of day continued to show a normal percentage.

CASE 1.—FRANK B.

Date.	Weight, kilos.	Food.				Urine.						Blood sugar, per cent. by weight.
		Total calories.	Carbohydrate, grams.	Fat, grams.	Food nitrogen, grams.	Volume, c.c.	Specific gravity.	Acidity, c.c. $N/_{10}$.	NH_3—N.	Total nitrogen, grams.	Glucose, grams.	
July												
2– 3	58.2	1847	50.5	139.9	13.6	1106	1032	510	0.60	15.49		
3– 4	57.7	1896	50.5	142.1	15.2	1360	1028	602	0.66	18.91	23.8	
4 –5	57.2	1903	14.9	147.5	19.2	2094	1023	785	0.86	22.98	24.2	
5– 6	56.9	1895	14.9	158.8	20.8	1895	1027	853	1.03	24.91	27.1	0.097
6– 7	56.7	2020	14.9	156.7	20.4	1705	1028	904	1.28	26.66	28.1	
7– 8	56.4	2046	14.9	158.2	20.4	1745	1025	873	1.43	26.90	25.8	0.105
8– 9	56.3	2064	14.9	159.2	20.8	1337	1032	769	..	25.4	27.9	
9–10	56.8	2064	14.9	159.2	20.8	1770	1024	717	..	24.5	26.0	0.102
10–11	56.5	2222	14.9	171.3	22.6	1845	1023	756	..	24.5	25.7	
11–12	55.8	2224	14.9	171.0	22.3	1330	1029	745	..	24.1	24.0	
12–13	56.2	2592	100.4	170.7	23.5	1620	1027	753	..	24.1	34.1	
13–14	55.8	2262	100.4	153.5	16.8	1024	1036	655	..	16.9	39.8	0.091
14–15	56.5	2262	100.4	153.5	17.4	1535	1026	629	..	14.7	35.0	
15–16	56.2	2262	100.4	153.5	16.8	1850	1022	620	..	17.6	30.6	0.081
16–17	56.1	2245	100.4	153.1	16.4	1815	1020	560	..	17.2	25.0	
17–18	55.9	2262	100.4	153.5	16.8	2125	1016	537	..	15.8	19.2	0.085
18–19	56.1	2254	100.4	153.7	16.4	1565	1023	614	..	16.6	22.3	
19–20	56.2	2261	100.4	153.7	17.4	1710	1022	654	..	16.7	24.4	0.092
20–21	56.1	2261	100.4	153.7	16.5	1280	1028	589	..	16.1	22.6	0.08
27–28	..	..	General ward diet			1850	..	..	..	..	34.4	
Aug.												
23–24	..	Practically unrestricted diet				1200	1033	726	..	19.6	30.9	
24–25	..	..	Fasting.	..	..	..	..	..	..	..	0.0	

The characteristics of renal glycosuria have been succinctly stated by Allen[2] as "glycosuria, with normal glycemia, relatively independent of diet." It is evident that the case described fulfils this definition precisely. In its chemical aspects it very closely resembles the case recently described by Lewis and Mosenthal.[3] With from 14 to 270 grams of carbohydrate in the diet the excretion of sugar in their case varied between 4.3 and 27 grams, the blood-sugar being normal.

There is one difference, however, which may be worthy of note, though we are not certain that it has any significance for this type of malady—namely, whereas it required six days of starvation to clear away sugar from the urine in their case, in ours it required only one day. At this time the young man had been living in the

[2] Glycosuria and Diabetes, Boston, 1913, p. 544.

[3] Bull. Johns Hopkins Hosp., 1916, xxvii, 133.

country and working as a gardener for one of the writers for about a month following the termination of the observations made in the hospital. He had improved markedly in strength, beginning with light work and increasing until he was able at the time mentioned to mow a rather large lawn without undue fatigue. On a diet containing oatmeal for breakfast, one slice of bread at each meal, and two glasses of milk, besides green vegetables and plenty of meat, his urine contained only 30.9 grams of glucose. This was the day before fasting. The fasting urine, begun at 7 A.M., twelve hours after his last meal, contained only the faintest possible trace of glucose, not more than is often found in normal urines.

The patient returned to the city October 1, 1916, and found work as a street-car conductor. His urine at this time contained a considerable amount of sugar, which was not quantitatively estimated.

CLINICAL STUDIES OF ACIDOSIS.

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and

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During the past few years much progress has been made in the study of the regulation of the body fluids as regards acidity and alkalinity and in the development of our conception of the condition known as acidosis.

Acidosis may well be compared with disturbance of the body temperature. It is recognized that life can continue only within a limited range of temperature variation and that health is compatible only with a still more restricted range. We are, more or less, familiar with the mechanisms which regulate the body temperature and maintain its constancy. Similarly, we have learned that the reaction of the body fluids as regards acidity and alkalinity must possess a degree of constancy even greater than must their temperature, if a normal condition or, indeed, life itself is to continue. Largely through the work of Lawrence Henderson,[1] and

[1] Clinical Studies on Acid Base Equilibrium and the Nature of Acidosis, Arch. Int. Med., 1913, xii, 153. Sellards, A. W., the Determination of Equilibrium in the Human Body between Acids and Bases, with Especial References to Acidosis and Nephropathies, Bull. Johns Hopkins Hosp., 1912, xxiii, 289.

his associates we have become familiar with at least some of the mechanisms by which this reaction is kept constant. The normal reaction in the body is maintained chiefly by three means: The first of these is the presence in the blood and lymph of the salts, chiefly the sodium salts, of two very weak acids, carbon dioxide and phosphoric acid. Of these two acids the former is the more abundant and important. In the blood and lymph, sodium carbonate (alkaline) and carbon dioxid (acid) are both present in such proportion as to give a nearly neutral reaction. Similarly disodium hydrogen phosphate (alkaline) and monosodium phosphate (acid) are both present in the proportions to give the same nearly neutral reaction. If to this almost neutral fluid a stronger acid, such as oxybutyric or lactic or hydrochloric acid be added, there occurs an interchange which diagrammatically may be expressed as follows: Each unit of strong acid combines with sodium of the salts of these weak acids, thereby liberating one unit of weak acid for each unit of strong acid introduced.

Sodium phosphate + hydrochloric acid = sodium chloride + phosphoric acid.

Sodium carbonate + hydrochloric acid = sodium chloride + carbon dioxid.

Thus for every unit of strong acid introduced into the blood there is liberated a unit of weak acid which possesses much less power of altering the reaction of the blood. The capacity of a free acid in a given concentration to alter the reaction of a fluid is dependent upon its ionization. For example, in a decinormal solution of hydrochloric acid, 91 per cent. of the hydrogen is dissociated in aqueous solution at ordinary temperature. Thus: $1000\ HCl = 910\ \overset{+}{H} + 910\ \overset{-}{Cl} + 90\ HCl$; on the other hand, in a decinormal solution of acetic acid only 1.3 per cent. of the reacting hydrogen is dissociated under similar conditions. Thus: $1000\ H(C_2H_3O_2) = 13\ \overset{+}{H} + 13\ \overset{-}{C_2H_3O_2} + 987\ H(C_2H_3O_2)$. Hence, a decinormal solution of hydrochloric acid although containing the same amount of reacting hydrogen as a decinormal solution of acetic acid is seventy times as strong an acid as the acetic acid, because the hydrogen ion concentration of the hydrochloric acid is seventy times as great as that of the acetic acid. The reaction, the color of an indicator added to a solution and in general the properties which we group under the term acidity are dependent upon the hydrogen ion concentration of the solution.

For the purpose of denoting the hydrogen ion concentration or reaction of a solution the notation now generally used in medical work is the logarythmic notation. In this notation the hydrogen ion concentration of a neutral solution is about 7; increasing degrees of acidity are indicated by decreasing figures and increasing degrees of alkalinity by increasing figures. By this notation the reaction of

urine ranges, according to Henderson and Palmer,[2] depending upon the character of the diet and other factors between the acid urine 4.7 and the alkaline urine 8.7. As a rule, it lies between 5 and 7.5. The blood possesses a very constant reaction at 7.4.

The first factor, therefore, in maintaining the constancy of reaction of the blood is the presence of considerable amounts of sodium carbonate with carbon dioxid and of sodium phosphate in the blood. When acids are added to the blood they combine with this sodium and liberate carbonic and phosphoric acids, both having very low coefficients of dissociation, hence producing a minimal change in the hydrogen ion concentration of the blood. This factor alone is extremely potent in diminishing the changes in the reaction of the blood and body fluids when subjected to the addition of acids or alkalies. The second and third factors are the rapid elimination from the body of these weak acids when so liberated, the phosphoric acid being eliminated by the kidney and the carbonic acid by the lungs. To these weak salts constituted with the weak acids, the sodium phosphate and sodium carbonate, Henderson has given the name "buffer substances," because of their effect in limiting the changes in reaction that would follow the introduction of acids or alkalies into the blood. As a result of their presence in the body fluids and of the rapid elimination by the lungs and kidneys of the carbonic acid and phosphoric acid liberated from them the blood and body fluids always preserve that constancy of reaction essential to life. It must be clear, however, that the continued introduction of acids into the blood will tend to reduce the amount of these buffer substances available, and must invariably do so if their depletion exceeds the body's capacity for replacing them. When such a reduction in the buffer substances of the blood has occurred the condition is that known as "acidosis." Acidosis may be defined as any condition in which the buffer substances of the blood and body fluids are reduced below the normal. The primary effect of such a reduction is a diminution in the capacity of the blood to transport acids or alkalies. The acid most abundantly produced in the body is carbonic acid, and when there is a reduction of the buffer substances of the blood there is a reduction in the blood's capacity for carrying carbonic acid. If this be marked enough there occurs an accumulation of carbonic acid in the tissues, and among other tissues in the respiratory center. As is well known, any increase of the acidity in the respiratory center, such as will be induced by an accumulation of CO_2, serves as stimulant to this center. A more thorough ventilation of the lungs results. A more thorough ventilation of the blood follows, and this favoring the removal of the CO_2 from the tissues, limits its further accumulation. Hence, an equilibrium

[2] Extreme Variations of the Concentration of Ionized Hydrogen in Human Urine, Jour. Biol. Chem., 1913, xiv, 81.

is established as a result of the response of the respiratory center to the carbon dioxid stimulation, and there is maintained an increased respiratory activity with more thorough ventilation of the lungs. This adjustment gives us one clinical symptom of acidosis, namely, hyperpnea, and one of our laboratory methods for detecting acidosis, namely, the reduction in the carbon dioxid concentration of the alveolar air; the latter, of course, being used as a measure of the thoroughness of pulmonary ventilation. Since the carbon dioxid tension of the alveolar air is, at least under normal conditions of the lungs, equal to the carbon dioxid tension of the arterial blood leaving the lungs, this increased ventilation of the lungs with lowering of the carbon dioxid tension of the alveolar air leads also to a lowering of the carbon dioxid tension of the arterial blood. It is well to emphasize the distinction between carbon dioxid tension and carbon dioxid content of a fluid or atmosphere. Like any other gas, carbon dioxid, whether in the air or dissolved in fluid, is present at some definite pressure or tension. In air the relation between the percentage of carbon dioxid and its pressure or tension is a simple one. Its pressure bears the same proportion to the total pressure of the air that its volume does to the total volume of the air. Thus, if carbon dioxid constitutes 6 per cent. of a sample of air, and that air is at atmospheric pressure (barometric pressure), which at the time is, let us suppose, 765 mm. of Hg., then the carbon dioxid tension in the sample of air will be 6 per cent. of 765, or 45.9 mm. Hg. The carbon dioxid of the alveolar air may be expressed either in per cent. or in mm. of Hg. tension, usually the latter. The carbon dioxid tension of a fluid is the pressure which the carbon dioxid exerts at the surface of the fluid. It is measured by determining the carbon dioxid which must be maintained in an atmosphere in contact with the fluid in order to keep the carbon dioxid content of the fluid unchanged. If the carbon dioxid tension of the atmosphere contiguous to a fluid is greater than that of the fluid the fluid absorbs carbon dioxid until the tension in each is equal, and *vice versa*. The amount or percentage of carbon dioxid, however, which a fluid must contain to possess a certain carbon dioxid tension varies greatly, depending upon the nature and temperature of the fluid. This is illustrated in the following table, giving the approximate carbon dioxid content and carbon dioxid tension of distilled water, a sample of blood and of serum at 38°. If acid be added to any fluid the carbon dioxid content of the fluid will be decreased for any given carbon dioxid tension. Reduction of the temperature increases the carbon dioxid content for any given carbon dioxid tension.

It is, of course, the carbon dioxid tension, not content, of alveolar air and of arterial blood which are equal. In some of the discussions of this subject it has been stated that in acidosis the carbon dioxid tension of the blood is decreased. This statement is open to criticism. In acidosis the total carbon dioxid content of the

blood (carbonate plus free carbon dioxid) is decreased; the amount of CO_2 that the blood can carry at a given CO_2 tension is decreased. As a result of stimulation of the respiratory center the pulmonary ventilation is greater, hence the CO_2 tension of the alveolar air and hence of the arterial blood is lower than normal; but, however much the total carbon dioxid content of the blood, arterial and venous, is reduced following the introduction of acids into the blood, and however much the carbon dioxid tension of the arterial blood is decreased by the increased respiratory activity, there is no proof that the carbon dioxid tension of the venous blood is decreased; indeed, it is possible that it may even be increased. Adequate studies upon this point are difficult, and are not yet available. Until the last few months only the very indirect method of gauging the existence of acidosis, namely, the determination of the thoroughness of pulmonary ventilation by estimating the carbon dioxid content or tension of the alveolar air, was our best laboratory method for the recognition of acidosis. The technic of this method has been greatly simplified recently by Marriott,[3] so that it may be carried out at the bedside in about five minutes' time and without any complicated apparatus. The value of this method has always been limited, however, first, by the fact that as a guage of the state of the blood it is dependent upon a normal irritability of the respiratory center. A hyperirritability of the respiratory center will maintain an increased pulmonary ventilation and a lowered alveolar CO_2 content without there being any acidosis, and conversely a diminished irritability of the respiratory center may diminish the evidence by this method of an existing acidosis. In the second place an alteration in the pulmonary ventilation may readily occur from unintentional alteration by the patient of his manner or rate of breathing during the time of examination. Moreover, in certain conditions, such as Cheyne-Stokes breathing, the pulmonary ventilation is variable and in pulmonary disease, such as pneumonia, we do not yet know what effect the local disease has upon the relation between the pulmonary ventilation and the state of the blood.

AMOUNT OF CO_2 IN VOLUMES PER CENT. HELD IN DISTILLED WATER, IN A SAMPLE OF WHOLE BLOOD (BOHR) AND IN A SAMPLE OF SERUM (JACQUET) AT THE SAME TEMPERATURE, 38°, AND THE INDICATED CO_2 TENSIONS.

CO_2 tension in mm. Hg.	Volumes per cent. of CO_2 in Water, per cent.	Whole blood, per cent.	Serum, per cent.
15 mm.	1.1	30.5	47.2
30 mm.	2.2	38.9	62.1
50 mm.	3.7	45.3	64.6

Fortunately, for the progress of our knowledge of acidosis, two methods have been given us during the past year which enable

[3] The Determination of Alveolar Carbon Dioxid Tension by a Simple Method, Jour. Am. Med. Assn., 1916, lxvi, 1594.

us to study directly from the blood itself the "buffer value" of the blood. The first devised by Van Slyke, Stillman, and Cullen[4] is a method for measuring directly by means of a special gas buret the amount of the sodium carbonate buffer in the blood. The second, devised by Levy, Rowntree, and Marriott,[5] is a method for gauging the same factor indirectly by determining the hydrogen ion concentration of a sample of the blood under certain conditions.

The first of these methods has been used by us in a series of clinical cases, and the results of these studies are here presented, together with some considerations concerning certain features of the technic.

The principle of this method is to obtain blood from the patient, oxalte it, separate the plasma and subject the latter to an atmosphere of definite carbon dioxid content or tension, about 6 per cent. (45 mm. tension). When the plasma has been brought into equilibrium with this atmosphere 1 c.c. of the plasma is transferred to a special gas buret, and by means of acid and a vacuum all the CO_2 held as carbonate is liberated and the total CO_2 drawn from the plasma into the vacuum and measured. The total CO_2 content after reduction to 0°, 760 mm. pressure, and correction for vapor tension, may be expressed as volumes per cent. of the original plasma. Thus, 1 c.c. of normal human plasma so treated will yield about 0.70 c.c. of CO_2, or seventy volumes per cent.

Technic. Upon first using this method we employed oxalated plasma obtained in the usual way by centrifuging the oxalated blood in open centrifuge tubes. The results secured were frequently surprising, however, and especially the remarkable variations often observed in repeated examinations of the blood of the same individual at different times. Investigation of the various steps in our procedure showed that these irregularities were due to the fact that the carbon dioxid binding capacity of a plasma is greatly influenced by the carbon dioxid tension present in the whole blood at the moment the cells and plasma are separated. If the carbon dioxid tension of the whole blood be high at the time of the separation into cells and plasma the plasma will have a higher binding capacity for carbon dioxid at any given tension than if the carbon dioxid tension of the whole blood be low at the time of the separation. This relation first pointed out by Zuntz[6] has been subsequently more thoroughly investigated by Guerber[7] and Petry.[8]

[4] Nature and Detection of Diabetic Acidosis, Proc. Soc. Exper. Biol. and Med., 1915, xii, p. 165.

[5] A Simple Method for Determining Variations in the Hydrogen ion Concentration of the Blood, Arch. Int. Med., 1915, xvi, 389.

[6] Bohr, C., Blutgase und respiratorischer Gaswechsel. In Nagel, W.: Handb. der Physiol. des Menschen, 1905, i, 116. Zuntz: Beiträge zur Physiologie des Blutes, Inaug. Diss., Bonn, 1868.

[7] Ueber den Einfluss der Kohlensäure auf die Verteilung von Basen und Säuren zwischen Serum und Blutkörperchen, Sitzbericht. d. phys. med. Gesellschaft z. Wurzburg, 1895–96, p. 28.

[8] Ueber die Verteilung der Kohlensäure im Blute, Beiträge z. chem. Phys. und Path., Hofmeister, 1902–3, iii, 247.

By these observers it was shown that when CO_2 escapes from the plasma of whole blood and leaves behind the base chiefly sodium, with which it has been combined, thus increasing the alkalinity of the plasma, a diffusion of hydrochloric acid occurs from the cells into the plasma to combine with at least a part of this free base. If this plasma is now separated from the cells its combining power for CO_2 is obviously less than that of the original plasma, since a portion of its base originally capable of holding CO_2 is now combined with hydrochloric acid diffused from the cells. When the whole oxalated blood is drawn and centrifuged in the ordinary way in open tubes a variable escape of CO_2 occurs during the process, and consequently from the same portion of blood, plasmas of very different binding capacities may be secured. It is in our experience highly important that either the escape of CO_2 from the blood be prevented from the time the blood is drawn until the removal of the plasma from the cells, or else that the blood be brought to some standard carbon dioxid tension at the time of centrifuging and kept at this tension until the plasma is separated. We are indebted to Dr. Van Slyke[9] for the suggestion of a simple method for securing the former of these two conditions. This consists of drawing the blood directly from the patient's vein through tubing which passes to the bottom of a centrifuge tube containing a few oxalate crystals and which ends beneath a layer of paraffin oil. The oil floating above the blood effectually prevents the escape of CO_2 until the centrifuging is complete and the plasma pipetted off. This paraffin oil method has been our standard method in these studies. In some cases, however, we have also saturated the whole oxalated blood at a tension of 6 per cent. CO_2 and kept it at this tension by stoppering or by covering with paraffin oil during the centrifuging.

To show the importance of this step we obtained in a series of seventeen cases the oxalated plasma from the whole blood in three ways: (1) blood drawn from the vein directly into a centrifuge tube beneath paraffin oil and hence protected from loss of CO_2 until removal of the plasma; (2) blood drawn and oxalated, exposed to the air, but subsequently saturated at 6 per cent. CO_2 tension and kept at this tension during centrifuging; (3) blood drawn, oxalated, and centrifuged in the ordinary way exposed throughout to the air. The plasmas obtained in these three ways were all saturated at 6 per cent. CO_2 tension and analyzed for their CO_2 content by Van Slyke's method. The results are shown in Table I, A. It will be seen that the paraffin oil and the 6 per cent. saturation of the whole blood give closely parallel results, the latter, as a rule, yielding a plasma that holds from 3 to 6 more volumes per cent. of CO_2. On the other hand the exposed blood

[9] Personal communication.

invariably yields a plasma of lower binding capacity, but in different individuals or in the same individual at different times the resulting plasma may be only one volume per cent. lower, or as much as 24 volumes per cent. lower.

TABLE I.—PART A.—THE EFFECT OF THE CO_2 TENSION OF THE WHOLE BLOOD UPON THE CO_2 CAPACITY OF THE PLASMA DERIVED FROM IT.

Case No.	CO_2 content of plasma saturated at 45 mm. CO_2 tension, the whole blood having been: Kept under paraffin oil. P.	Saturated at 45 mm. CO_2 at 20° C. S.	S–P.	Exposed to air. E.	P–E.
1	73	77	4	50	23
2	73	72	–1	51	22
3	70	66	–4	68	2
3	66	68	2	49	17
4	66	70	4	49	17
5	65	68	3	49	16
6	64	73	9	48	16
7	64	68	4	57	7
8	64	68	4	43	21
8	62	68	6	50	12
9	62	68	6	59	3
10	60	64	4	55	5
11	59	62	3	38	21
12	53	59	6	43	10
13	52	58	6	44	8
14	51	49	–2	38	13
14	46	48	2	45	1

If the oxalated blood before centrifuging be thoroughly aerated by being poured from beaker to beaker for five minutes the resulting plasma exhibits a still lower CO_2 capacity, as shown in Table I, B.

PART B.

Case No.	Kept under paraffin oil. P.	Aerated 5 minutes A.	P–A.
15	70	48	22
16	70	59	11
17	66	47	19
18	65	46	19
19	64	49	15
20	61	44	17
21	58	51	7

At first sight it might seem surprising that saturation of the whole blood at 6 per cent. (45 mm.) CO_2 tension should increase the CO_2 capacity of the plasma as compared with the blood as drawn from the vein under paraffin oil. That this occurs is due to the fact that the saturation of the whole blood at 45 mm. tension was carried out at room temperature (18° to 20° C.), and the blood will, as a rule, hold more CO_2 at 18° C. at 45 mm. tension than at the same or higher tension that exists in the veins at 37° C.

Effects of Cyanosis. In considering the relative merits of the paraffin oil method and the 6 per cent. saturation of the whole

blood in the study of acidosis it will be recognized that most factors will alter the plasma in the same direction and about equally whichever of these methods be used. One conspicuous exception to this relation exists, however, namely, any alteration in the CO_2 tension of the venous blood as drawn, such, for example, as occurs in asphyxia or cyanosis. This may be seen in the experiments shown in Table II.

TABLE II.—EFFECT OF INJECTION OF ACID, ALKALI, AND OF ASPHYXIA ON THE CO_2 CAPACITY OF THE PLASMA.

Dog No.	Blood drawn after:	CO_2 content of plasma saturated at 45 mm. CO_2 tension, the whole blood having been Kept under paraffin oil. P.	Saturated at 45 mm. CO_2 at 20° C. S.	S– P.
1	Control period	54	56	2
	KH_2PO_4	47	52	5
	Asphyxia	48	46	−2
	Na_2CO_3	67	70	
2	Control period	52	62	10
	Asphyxia	55	58	3
	KH_2PO_4	48	58	10

These experiments were performed to show the effect upon the CO_2 binding capacity of the plasma of injection of alkalies, of injection of acids, and of increase in the CO_2 tension of the venous blood from asphyxia.

Experiment I. A normal dog, weighing 10 kilos, was etherized; 10 c.c. of blood drawn and oxalated under paraffin oil from the right jugular vein and immediately a second portion of 10 c.c. drawn and oxalated exposed to the air for subsequent saturation as whole blood at 6 per cent. CO_2 (control blood). There was then injected in the course of fifteen minutes 150 c.c. of KH_2PO_4 solution (13.6 gms. per liter) into the left femoral vein. Two portions of blood were immediately taken from the right jugular vein as before (KH_2PO_4 blood). The trachea was then compressed until the tongue was deeply cyanosed and two more portions of blood taken as before from the right jugular vein (asphyxia blood). After a few minutes' interval 150 c.c. of 3 per cent. Na_2CO_3 solution was injected in fifteen minutes into the left femoral vein and two portions of blood taken as before from the right jugular vein (Na_2CO_3 blood). The injection of acid phosphate reduced the CO_2 capacity of the plasma obtained both by the paraffin oil and by the 6 per cent. saturation method. Asphyxia still further reduced the CO_2 capacity of the plasma by the 6 per cent. saturation method, but slightly increased that of the plasma from the paraffin oil method. Thus a slight acidosis of asphyxia was wholly obscured by the increased CO_2 tension of the venous blood when the plasma was obtained by the paraffin oil method.

Experiment II. This experiment is identical, except that the asphyxia was performed before the injection of the acid phosphate.

The results are similar, but perhaps even more striking. Whether this effect of asphyxia upon the plasma obtained by the paraffin oil method would ever be of clinical importance is not certain, but in a very cyanotic patient it is possible.

Van Slyke Method in Clinical Cases. A series of clinical cases chosen more or less at random have been studied by the Van Slyke method, using the paraffin oil method for obtaining the plasma. The results are shown in Table III. Throughout this study all figures are the volumes of CO_2 per cent. reduced to 0° C., 760 mm. and corrected for vapor tension. It has seemed to us that the normal limits by this method may be considered as lying between 65 and 80 volumes per cent. Between 55 and 65 volumes per cent. the patients have been, as a rule, mildly nephritic, mildly diabetic, or markedly arteriosclerotic, and might, therefore, be expected to exhibit the slightest grade of acidosis. Below 55 the patients have been for the most part advanced nephritics, except for one moderately severe diabetic and one quite septic case.

Comparison of Three Methods. In a series of cases we have compared the carbon dioxid capacity of the plasma obtained under paraffin oil, the alveolar air, using the Plesch-Higgins method[10] and the hydrogen ion concentration of the serum by the dialysis method of Levy, Rowntree, and Marriott after blowing off the free CO_2 from the dialysate as recently suggested by Marriott. The results are shown in Table IV. In general the results agree, but the method of Van Slyke is distinctly the most sensitive of the three and gives much more perfect duplicates than does the method of alveolar air.

Van Slyke Method Following Anesthesia. The Van Slyke method has been applied to the study of a few cases following nitrous oxide-ether anesthesia. The results are shown in Table V. It will be seen that after from thirty to one hundred and fifteen minutes, ether anesthesia, a lowering of the CO_2 capacity of the plasma, was constantly observed. The degree to which it was lowered was, in general, proportional to the duration of the anesthesia. In a thirty minutes' anesthesia the lowering was only two to four volumes per cent. while in an anesthesia of one hundred and five minutes it was reduced to forty-nine volumes per cent., about fifteen below the normal. The reduction is apparently at or near its maximum at the close of the anesthesia and exhibits no marked changes in either direction for the next four or five hours, perhaps for twenty-four hours. The time required for return to normal has not been determined.

In eight of ten cases in which the urine was studied, acetone was studied by the sodium nitroprusside test in the first or second twenty-four hours after operation. The ferric chloride test was positive once. Even when the acetone test was strongly positive, however, the total ketone bodies were never present in more than

TABLE III.—CLINICAL CASES. CO_2 CONTENT OF PLASMA (BLOOD TAKEN UNDER PARAFFIN OIL).

No.	Diagnosis.	Age.	Date.	Plasma CO_2.	Alveolar CO_2.	Blood-pressure.	Blood urea, nitrogen.	Ketonuria gms. per 24 hours.
	Controls:							
1	Headache	.....	.....	78				
2	Carcinoma of lip	.....	.....	78				
3	Sprain	.....	.....	71				
4	Angioneurotic edema	.....	.....	71				
5	Sarcoma of leg	.....	.....	71				
6	Papilloma of bladder	.....	.....	70				
7	Pneumonia	.....	.....	69				
8	Varicocele	.....	.....	65				
9	Hemorrhoids	.....	.....	65				
10	Fracture of arm	.....	.....	65				
11	Myoma uteri	.....	.....	65				
12	Gastric neurosis	.....	Feb. 22	70				
	Gastric neurosis	.....	Feb. 26	64				
	Gastric neurosis	.....	Feb. 28	66				
13	Endothelioma	.....	Feb. 5	63				
	Endothelioma	.....	Feb. 8	65				
	Arteriosclerotics:							
14	Arteriosclerosis	57 years	.....	68	..	142–85	14	
15	Arteriosclerosis	60 years	.....	66	..	150–85		
16	Arteriosclerosis	49 years	.....	66				
17	Arteriosclerosis	59 years	Feb. 27	65	..	170–120	17	
			Mar. 9	71	..	170–120	29	
18	Arteriosclerosis	63 years	Mar. 16	61	..	230–130		
			Mar. 29	63	..	230–130		
19	Arteriosclerosis	56 years	.....	62	..	220–135	14	
20	Cerebral hemorrhage	.....	.....	60				
21	Atrophic cirrhosis	56 years	.....	57	..	160–120	13	
	Nephritics:							
22	Early nephritis	36 years	.....	72	..	176–110	17	
23	Chronic nephritis	42 years	.....	64	..	.....	33	
24	Early nephritis	24 years	.....	62	..	198–150	14	
25	Parenchymatous nephritis	21 years	Apr. 17	61	..	150–110	17	
			Apr. 19	63	..	150–110		
			May 6	64	..	150–110	16	
			May 15	69	48	135–90		
26	Chronic nephritis	15 years	.....	59	..	165–115	23	
27	Chronic nephritis	45 years	.....	59	..	185–135	18	
28	Acute nephritis	30 years	Apr. 12	53	30	115–65	35	
			Apr. 27	77	55	115–65	13	
29	Chronic nephritis	26 years	.....	53	..	140–100	21	
30	Advanced nephritis	44 years	Feb. 25	51	..	180–140	67	
			Mar. 4	46	..	180–140	49	
			Mar. 8	46	..	180–140	51	
31	Advanced nephritis	39 years	Apr. 17	48				
			Apr. 27	55				
			May 6	48	..	.....	116	
			May 12	46	35	.....	119	
32	Advanced nephritis	55 years	.....	37	33	190–100	142	
33	Advanced nephritis	56 years	.....	35	25	158–80	122	
34	Advanced nephritis	34 years	Mar. 27	40	..	178–115	195	
			Mar. 29	33	..	178–115		
	Mercurial nephritis:							
35	Bichloride poisoning (severe)	21 years	June 6	70	..	120–75	16	
			June 7	70	..	120–75	20	
			June 15	71	..	120–60	17	
36	Bichloride poisoning (mild)	24 years	June 12	70	..	115–70	14	
			June 15	70	..	120–75	13	
	Eclampsia:							
37	Eclampsia	.....	.....	57	..	.....	21	
38	Eclampsia	.....	.....	52	..	.....	29	
39	Eclampsia	.....	.....	52	35	.....	20	
40	Eclampsia	.....	.....	48	..	.....	13	
41	Eclampsia	.....	Mar. 28	46				
			Mar. 30	57	..	.....	14	
	Septic:							
42	Pelvic inflammation	32 years	Feb. 29	52	..	195–120	12	
			Mar. 27	63				
	Diabetes:							
43	Mild	18 years	.....	71	..	.....	...	2.0
44	Mild	25 years	.....	64	..	.....	...	0.4
45	Mild	51 years	.....	60	..	.....	...	2.0
46	Mild	35 years	Mar. 8	52	..	.....	...	4.6
			Mar. 29	64	..	.....	...	0.4

The blood urea nitrogen estimations in the table were performed by the urease method (Van Slyke and Cullen); the urinary ketones by Schaffer's method.

very small amounts, the largest amount excreted in twenty-four hours being 0.83 mgm. expressed as acetone (Shaffer's method). The total acid output by Henderson's and Palmer's method was normal.

TABLE IV.—COMPARISON OF CO_2 CONTENT OF PLASMA, CO_2 TENSION OF ALVEOLAR AIR AND HYDROGEN ION CONCENTRATION OF SERUM AFTER AËRATION OF DIALYSATE.

Case No.	CO_2 content plasma.	CO_2 tension alveolar.	Hydrogen ion of serum.
1	77	44	8.1
2	72	50	8.0
3	69	48	8.0
4	67	43	8.0-
5	65	50	7.9
6	64	39	8.0
7	63	41	8.0
8	62	38	8.1
9	58	44	8.1
10	52	40	8.0
11	52	35	7.9
12	46	35	7.9
13	37	33	7.7

TABLE V.—EFFECT OF ETHER ANESTHESIA ON CO_2 CONTENT OF PLASMA.

Case No.	Operation.	Age.	Duration of anesthesia, minutes.	CO_2 content: Before.	After.
1	Carcinoma of lip	72	30	73	69
2	Amputation of leg	17	30	70	66
3	Amputation of leg	30	30	65	63
4	Herniorrhapy	20	35	..	64
5	Hemorrhoids	19	35	65	59
6	Perineal, plastic	51	40	..	56
7	Nephrotomy	30	50	..	60
8	Ectopic pregnancy	35	50	..	53[10]
9	Nephrotomy	48	70	..	59
10	Perineal, plastic	46	85	..	47[10]
11	Suprapubic cystotomy	24	90	70	60
12	Pan hysterectomy	56	100	..	53[10]
13	Pan hysterectomy	58	105	..	51
14	Pan hysterectomy	19	105	..	49[10]
15	Pan hysterectomy	35	110	65	57
16	Gastrojejunostomy	39	115	..	56

Four of the patients received just at the close of the anesthesia two pints each of 5 per cent. glucose solution per rectum. These cases showed quite as marked a reduction of the carbonate content of the plasma as did comparable cases not receiving the glucose.

The cause of acidosis is different in different conditions. In diabetes it is due largely to the presence in the blood of the ketone acids. In nephritis and severe diarrhea it is probably, according to Howland and Marriott,[11] due to an impaired capacity on the

[10] Received glucose per rectum at close of anesthesia.

[11] Acidosis Occurring with Diarrhea, Am. Jour. Dis. of Child., 1916, xi, 309.

part of the kidneys to excrete phosphoric acid. For other types the cause of the acidosis is not known. That the clinical symptomatology varies somewhat with the type and cause of the acidosis is apparently true. Whether the treatment of acidosis, *per se*, apart from its cause will be of importance remains to be determined. Henderson has urged that in any conditions associated with reduction in the buffer value of the blood, sodium bicarbonate be given by mouth to the point of rendering the urine less acid, but not distinctly alkaline. Using this simple criterion one may endeavor to replenish the supply of buffer substances in the blood and yet avoid overtaxing the system with excessive alkali. In this connection attention may be called to the suggestion of Magnus-Levy[12] that in giving sodium carbonate solutions intravenously for the treatment of severe acidosis the injection of a highly alkaline solution may well be a severe insult to the system. He suggested that a safer plan is to pass CO_2 gas through the sterile sodium carbonate solution, to which a drop of phenolphthalein has been added, until the solution is colorless, when it becomes more closely analogous to the normal sodium carbonate-carbon dioxid buffer of the blood —the reaction of which is nearly neutral—the substance which one is aiming by such injections to replace.

Conclusions. 1. In the new methods for studying acidosis directly from the blood we have a means of investigation that constitutes a distinct advance upon our previous methods.

2. As criteria of the supply of "buffer substance" in the blood the carbon dioxid capacity of the plasma (Van Slyke, Stillman, and Cullen method) the hydrogen ion concentration of the serum (Levy, Rowntree, and Marriott method) and the alveolar air (Plesch-Higgins method) give results that are in general parallel. The first of these is the most sensitive of the three and gives much more satisfactory duplicates than does the alveolar air determination. It affords a simple and quick method of determining the presence and degree of acidosis.

3. In using the method for the CO_2 capacity of the plasma, and presumably in any method intended to measure directly or indirectly the alkalinity of the plasma, the CO_2 concentration of the whole blood must be kept unchanged or brought to a standard tension while centrifuging and separating the plasma from the cells.

4. Asphyxia or any condition of high CO_2 tension in the blood *in vivo* raises the CO_2 capacity of the plasma if the latter is separated by the paraffin oil method, and may interfere with the recognition of a slight acidosis. This may be overcome by saturating the whole blood at a standard CO_2 tension before centrifuging and maintaining this tension until the plasma is pipetted off.

[12] Ueber subkutane Infusionen von Mononatriumkarbonat, Thçrap. Monatsch., 1913, xxvii, 838.

5. By the Van Slyke method the normal CO_2 capacity of the plasma reduced to 0° 760 mm. pressure and correcting for vapor tension appears to be about sixty-five to eighty volumes per cent. This is slightly reduced in arteriosclerotic conditions and moderately to markedly reduced in diabetes and nephritis, especially in the advanced stage.

6. After ether anesthesia there is a depression of the CO_2 capacity of the plasma of from two to twenty volumes per cent. This depression is proportional to the duration of the anesthesia. The lowest figure observed was 47. This reduction is present and probably maximal at the close of the anesthesia, and apparently remains little altered for at least five hours. A single injection of two pints of a 5 per cent. glucose solution per rectum at the close of the anesthesia does not lessen the reduction in the CO_2 capacity during the next five hours.

THE TOXEMIAS OF PREGNANCY.

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AND

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Although no general agreement has been reached concerning the nature of the substances causing the toxemias of pregnancy, two explanations have claimed special consideration. Ewing and Wolf,[1] noting the anatomical changes of the liver in eclampsia, the facts that leucine and tyrosine had been reported in eclamptic urines, and that they themselves found often a decrease in urea and an increase in the "undetermined nitrogen" fraction of the urine, suggested that the amino-acids were incompletely catabolized in the degenerated liver, and were the cause of both the toxemia and the abnormal nitrogen distribution. Later Murlin and Bailey,[2] also working in the Cornell laboratory, attacked the same problem with the aid of Soerensen's formol titration method, which is specific for amines and amino-acids. They decided that not only the amino-acid fraction, but also the other nitrogen fractions of the urine are likely to be within the limits of normal variation both before and immediately after the convulsions of eclampsia, and that consequently the nitrogen distribution in the urine offers no reliable

[1] Am. Jour. Obst., 1906, lv, 289.
[2] Jour. Am. Med. Assn., 1912, lix, 1522.

means for either diagnosing the preëclamptic state or indicating the nature of the toxin.

The other explanation is that abnormal acids in the blood are responsible for the toxemia. It is known that even in normal pregnancy a slight degree of acidosis is indicated by the carbon dioxide content of the alveolar air,[3] and it was not illogical to suggest that an intensification of the acidosis might be a factor in the cause of eclampsia. Zweifel[4] not only designated acidosis as the cause of eclampsia, but identified the specific acid as sarcolactic. This he found to be three times as concentrated in blood from the umbilical cord as in the venous blood of the mother, and he interpreted the results as proof that the mother is intoxicated by lactic acid formed in the fetus. Hasselbalch and Gammeltoft[5] found also that in two out of four cases of eclampsia examined by them the "regulated" hydrogen ion concentration of the blood was abnormally high, the values for pH at normal CO_2 tension being 7.17 and 7.22 instead of the normal 7.45.

It seemed to the writers desirable to test the acidosis hypothesis quantitatively on a number of cases in order to ascertain whether a degree of acidosis unusual for pregnancy regularly accompanies eclampsia, and whether the intensity of the acidosis is sufficient to account for the symptoms and ultimate coma noted. It seemed also not without interest to test with the gasometric method the proportion of amino-acid nitrogen in the urine in eclampsia, since the results of previous investigations on amino-acids in the urines of pregnancy, which have been performed with the help of the formol titration method, have not been entirely in agreement. While Hasselbalch and Gammeltoft found the proportion of amino-acid nitrogen normal (2 to 3 per cent. of the total nitrogen) in normal pregnancy, Falk and Hesky, with the same method, report results running chiefly between 3 and 7 per cent., 73 per cent. of the cases showing figures above the ordinary limits observed in non-pregnant women. Falk and Hesky also noted in pregnancy a similar increase in peptide nitrogen, which varied from 2 to 7 per cent., non-pregnant women showing figures of from 1 to 2 per cent. Murlin and Bailey did not determine the peptide nitrogen, but found in their three cases of normal pregnancy amino-acid nitrogen figures of 3.3, 5.1, and 4.3 per cent. of the total nitrogen, figures which, like those of Falk and Hesky, are somewhat above the normal.

We have determined in the urine the "total amino-acid nitrogen,"[6] which includes the nitrogen of the free amino-acids and also that of the amino-acids conjugated in such forms as peptides and hippuric acid. In normal individuals this nitrogen runs from 1.5 to

[3] Hasselbalch, K. A., and Gammeltoft, S. A., Biochem. Ztschr., 1915, lxviii, 207.
[4] München. med. Wchnschr., 1906, liii, 297. [5] Loc. cit.
[6] Levene, P. A., and Van Slyke, D. D., Jour. Biol. Chem., 1912, xii, 310; 1913, xvi, 125.

3.5 per cent. of the total nitrogen. Consequently the excretion of any considerable amount of amino-acids either free or conjugated would cause a marked rise in this figure. We have also determined the proportion of the total nitrogen in the form of urea, ammonia, and albumin.

As a further index of the amino-acid metabolism we have determined in a number of cases the amino-acid nitrogen of the blood[7] since the blood can be expected, even before the urine, to show evidence of failure of the organism to metabolize amino-acids with normal efficiency. The total non-protein nitrogen and urea nitrogen were also determined in most of the blood analyses.

As a measure of acidosis we have determined the volume percentage of carbon dioxide bound in the form of bicarbonate by the blood plasma.[8] Since all the reserve alkali of the blood, *i. e.*, the alkali in excess of that combined with acids other than carbonic, takes the form of bicarbonate, this figure indicates the alkaline reserve of the blood plasma, and in fact of the body as a whole.

Methods. Urea was determined in both blood and urine by Marshall's urease method in the form developed by Van Slyke and Cullen.[9]

Amino-acid nitrogen of the blood was determined after precipitation of the proteins by alcohol, as described by Van Slyke and Meyer.[10] The micro-amino apparatus was used, so that the determinations could be done on an amount of filtrate corresponding to 2 c.c. of blood. As shown by Greenwald[11] the proteins precipitated by alcohol adsorb a portion of the amino-acid nitrogen, but the proportion is so constant that for comparative purposes the method is accurate.

Total non-protein nitrogen of the blood was determined by Folin micro-Kjeldahl[12] determination on an aliquot portion of the alcoholic filtrate from the blood proteins.

Carbon dioxide capacity of the plasma was determined by Van Slyke's method.[13]

The albumin of the urine was determined by a modification of Welker's method[14] as follows: Twenty-five c.c. of urine were acidified with acetic acid and heated to coagulate the albumin. The volume of the solution was then brought to 50 c.c. by the addition of an aluminum hydroxide suspension, prepared as described by Welker for adsorption of proteins, and containing 0.5 per cent. of Al_2O_3. The mixture was shaken and filtered through a folded filter. The nitrogen content was determined by Kjeldahl on 4 c.c. of the

[7] Van Slyke, D. D., and Meyer, G. M., Jour. Biol. Chem., 1912, xii, 399.
[8] Van Slyke, D. D., Proc. Soc. Exper. Biol. and Med., April 21, 1915.
[9] Jour. Biol. Chem., 1914, xix, 211. [10] Loc. cit.
[11] Jour. Biol. Chem., 1915, xxi, 61.
[12] Jour. Biol. Chem., 1913, xi, 529. [13] Loc. cit.
[14] Tracy, G., and Welker, W. H., Jour. Biol. Chem., 1915, xxii, 55.

filtrate and on 2 c.c. of the untreated urine. The difference indicated the albumin nitrogen.

The use of the aluminum hydroxide alone, without previous coagulation of the mass of the albumin, proved insufficient to remove all the albumin from some of the urines in which it was especially abundant.

The total amino-acid nitrogen of the urine was determined on 25 c.c. of the albumin-free filtrate by the gasometric method previously described, the urea being destroyed and conjugated amino-acids set free by heating with dilute sulphuric acid in an autoclave.

The *ammonia* was determined by Folin's aëration method, 5 c.c. of saturated potassium carbonate solution being added to 5 c.c. of urine, and the ammonia aërated into 0.02 N hydrochloric acid.

Discussion of Results. *Acidosis.* Examination of between 20 and 30 normal plasmas by Van Slyke, Stillman, and Cullen,[15] and of 30 by Gettler and Baker[16] have shown that 100 c.c. of average normal plasma binds 65 c.c. of CO_2, no normal plasma showing a figure below 55 and very few above 75, the great majority lying in the range 60 to 70. Our 14 cases of normal pregnancy all showed figures below the average normal of 65, and 10 of them were observed on at least one day to show figures below the minimum normal of 55. Consequently we can agree with the conclusion reached as the result of their alveolar carbon dioxide determinations by Hasselbalch and Gammeltoft,[17] that a slight acidosis is usually present in even normal pregnancy.

Our cases of toxemia of both the eclamptic and vomiting type show little difference from normal pregnancy in their alkaline reserve. The same subnormal carbon dioxide is seen, but in no case does it approach so low a value as 30 c.c. of CO_2 per 100 c.c. of plasma, which experience with the acidoses of diabetes and nephritis indicates must be fallen below, before any but exceptional cases show serious distress from acidosis *per se*.

The blood from the umbilical cord showed a bicarbonate content in only one case significantly different from that of the mother's blood. The results give no support to the presumption that the fetus elaborates amounts of acid sufficient to cause acidosis in the mother.

It is noteworthy that although the cases of pernicious vomiting show strikingly high ammonia figures, the plasma bicarbonate indicates no greater degree of acidosis than may be observed in non-toxic pregnancy. A. W. Sellards[18] mentions similarly a case of toxemia of pregnancy in which 40 per cent. of the urinary nitrogen was ammonia, but in which other evidence excluded acidosis.

[15] Loc. cit.
[16] Jour. Biol. Chem., 1916, xxv, 211.
[17] Loc. cit.
[18] Johns Hopkins Hosp. Bull., 1914, xxv, 147.

Amino-acids. In only 3 of the 23 cases of toxemia in which amino nitrogen of the urine was determined was the figure above the 3.6 per cent., the maximum noted in a previous series of normal men. In the 3 cases where a higher figure was observed the amino nitrogen exceeded the usual limit by a margin smaller that the maxi-

TABLE I.—PLASMA BICARBONATE AND NITROGEN DISTRIBUTION OF URINE IN NORMAL PREGNANCY.

History.	Total N. g. per 100 c.c.	Urine.					C.c. of CO_2 bound by 100 c.c. of plasma.	
		Per cent. of total N. as:						
Para, months pregnant, etc.		Albumin.	Urea.	Ammonia.	Total amino-acids.	Undetermined.	Mother's blood.	Infant's blood.
Full term	1.168	..	75.8	5.8	..	..	57	
Full term	1.014	..	83.8	5.8	3.7	6.7	60	
2 days p. p.	0.782	..	83.2	4.4	2.6	9.8	54	
Full term	0.596	..	69.2	7.0	5.4	18.4	51	
1 day p. p.	0.963	..	75.8	6.7	3.7	13.8	61	
Full term;	..	..	..	..	..	..	53	51
2d blood; 2 days p. p.							54	
Full term;	..	..	..	..	..	..	51	56
2d blood; 3 days p. p.							62	
Full term;	..	..	..	..	..	..	49	52
2d blood; 3 days p. p.							58	
Full term;	..	..	..	..	..	..	50	53
2d blood; 3 days p. p.							63	

TABLE II.—NITROGEN DISTRIBUTION OF BLOOD AND URINE IN ECLAMPSIA.

History.	Non-protein N. of blood. Mg. per 100 c.c.			Urine.					
				Total N. g. per 100 c.c.	Per cent. of total N. as:				
Para, months pregnant, blood-pressure, etc.	Total.	Urea.	Amino acids.		Albumin.	Urea.	Ammonia.	Total amino acids.	Undetermined.
P. V, 8 mos., 230 b. p.; accouchment force; died, typical liver lesions	46	21	7.6	0.642	4.7	54.3	10.2	2.5	25.7
P. I, 8 mos., 248 b. p.; no convulsions nor coma; mild type	36	14	7.9	1.410	6.2	64.4	8.1	2.7	17.6
P. IV, 9 mos., 196 b. p.; semicomatose 7 days; died 5 days p. p.	31	10	7.9	0.784	20.9	46.1	3.1	3.2	26.7
P. I, 9 mos., 140 b. p.; semicomatose	26	15	4.0	0.610	10.1	56.2	3.2	2.5	28.0
P. I, 8 mos., 170 b. p.; marked edema	28	..	6.2	0.374	17.9	62.0	6.6	2.0	11.5
P. I, 7 mos., 170 b. p.; edema	25	..	7.8	1.195	4.1	66.2	10.1	2.3	17.3
P. I, 9 mos., 180 b. p.; no convulsions	28	..	5.0	0.633	16.3	51.2	10.2	3.1	19.2
P. I, 8 mos., 150 b. p.; died in coma, 6 days p. p.; first urine and blood 4 days p. p.; second 5 days p. p.	43	26	4.4	1.887	1.1	74.0	5.6	2.0	17.3
				2.275	7.7	72.0	4.6	1.5	14.2
P. I, 9 mos., 125 b. p.; moderate edema; coma; first specimen day of delivery; second one day p. p.	41	25	5.5	0.680	9.7	53.0	12.0	4.7	20.6
	41	26	4.3	0.795	1.9	74.5	7.4	3.5	12.7
P. I, 8 mos., 165 b. p.; edema; general condition fair	32	11	5.0	0.383	24.3	49.3	6.0	2.5	17.9

mum observed either by K. W. Wilson[19] or ourselves in normal pregnancy. The results confirm those obtained by Murlin and Baily with the formol method.

Not a single one of the 10 eclamptic women whose blood was examined for amino nitrogen showed a figure outside the range

TABLE III.—PLASMA BICARBONATE AND NITROGEN DISTRIBUTION OF URINE IN ECLAMPSIA.

History. Para, months pregnant, b. p., etc.	Total N. g. per 100 c.c.	Urine. Per cent. of total N. as: Albumin.	Urea.	Ammonia.	Total amino-acids.	Undetermined.	C.c. of CO_2 bound by 100 c.c. of plasma. Mother's blood.	Infant's blood.
P. I, 9 mos., 168 b. p.; convulsions	0.554	15.3	57.3	8.1	..	..	52	
P. I, 9 mos., 186 b. p.; blood and urine 48 hours p. p.; coma	1.595	..	..	..	2.6	..	54	
P. II, 24 hrs. p. p., 170 b. p.; eight convulsions; p. p. eclampsia	0.706	1.6	68.5	8.9	2.6	18.4	47	
P. III, 10 hrs. p. p.; 170 b. p.; p. p. eclampsia	0.530	29.2	..	7.9	1.6	..	46	
P. I, 8 mos., 186 b. p.; semicomatose; convulsions; blood 14 hrs. p. p.; urine 30 hrs. p. p.	1.090	3.2	65.7	7.4	2.5	21.2	45	
P. III, 7 mos., 220 b. p.; convulsions and edema	1.025	54.7	27.2	8.3	4.1	5.7	45	
P. VI, 9 mos., 160 b. p.; convulsions; blood and urine 2 days p. p.	0.449	+	75.9	4.5	2.2	17.4	58	
P. I, 8 mos.; convulsions; coma	0.639	Trace	63.3	11.3	4.6	20.8	43	47
P. III, 5 days p. p., 168 b. p.; p. p. eclampsia and convulsions	0.674	25.5	53.1	2.0	2.9	16.5	51	
P. I, 9 mos., 216 b. p.; no convulsions; first specimen one day before delivery; second labor day	0.215	+	56.8	6.0	..	..	47 41	32
P. I, 5 mos., 190 b. p.; preëclamptic	..	..	..	..	..	..	54	
P. —, 9 mos., 156 b. p.; semicomatose; convulsions	..	..	..	..	..	..	45	47
P. I, no convulsions; edema	..	..	..	..	..	..	47	45
P. I, 8 mos., 156 b. p.; coma	..	..	..	..	..	..	44	

TABLE IV.—PLASMA BICARBONATE AND NITROGEN DISTRIBUTION OF URINE IN PERNICIOUS VOMITING.

History. Para, months pregnant, b. p., etc.	Total N. g. per 100 c.c.	Urine. Per cent. of total N. as: Albumin.	Urea.	Ammonia.	Total amino-acids.	Undetermined.	C.c. of CO_2 bound by 100 c.c. of plasma. Mother's blood.
P. I, 3 mos., 140 b. p.; vomiting two weeks; much emaciated	0.782	1.5	54.8	24.9	2.4	16.4	
P. II, 3 mos.; vomiting one week	1.020	..	46.3	31.2	2.3	..	62
3 months	0.602	..	55.4	27.4	2.3	14.9	
2½ months	1.645	..	67.4	17.5	2.2	12.9	52
3 months	1.791	..	64.1	16.9			
P. II, 2½ mos.; vomiting four weeks; condition bad	0.928	Trace	51.1	29.0	2.9	17.0	41

[19] Johns Hopkins Hosp. Bull., 1916, xxvii, 121.

4 to 8 mg. per 100 c.c. noted by Ellis, Cullen and Van Slyke[20] in a series of normal men. In brief, neither blood nor urine of eclamptic women shows, as a rule, an amino-acid content above normal limits.

Inspection of the other nitrogen figures of the urine shows that the *urea in eclampsia* is usually below the average normal, often strikingly so, even if calculated on the basis of total nitrogen of the urine minus the albumin nitrogen. The only eclamptic urines which showed more than 70 per cent. of urea nitrogen were those obtained one or more days postpartum. The ammonia was often higher than the average in normal individuals, but the abnormality is less striking than that of the urea. The ammonia and urea ratios are suggestive of those which Nencki and Pavlov[21] obtained from dogs from which the livers had been removed.

All the cases of *pernicious vomiting* showed strikingly *high ammonia* percentages. It appears quite possible that this fact may be due, as pointed out by Underhill and Rand,[22] merely to fasting, and that Williams'[23] separation of pernicious vomiting cases into those of toxic and nervous origin, according as the urinary ammonia is high or low, is not justified. Regardless of its etiological significance, however, the frequency of the appearance of high ammonia in pernicious vomiting (none of our 6 cases showed less than 16.9 per cent.) must be admitted to give to the ammonia ratio an undoubted diagnostic value.

The above findings concerning the ammonia and urea ratios in eclampsia and pernicious vomiting confirm the results of Ewing and Wolf.[24]

In our 5 cases of non-toxic pregnancy the nitrogen ratios were normal.

Conclusions.—The toxemias of pregnancy can be attributed neither to failure in diaminization of the amino-acids, nor to the moderate degree of acidosis observed. The nature of the toxin or toxins therefore remains unknown.

The nature of the functional disturbances which cause the abnormal nitrogen metabolism observed also still awaits a satisfactorily conclusive explanation. Nevertheless the constancy of the low urea ratios in the urine in eclampsia, and of high ammonia in pernicious vomiting, lends decided support to the opinion of Ewing and Wolf, that the nitrogen distribution of the urine, considered "in connection with all the data in the case," should assist in diagnosing the toxemias of pregnancy, and in differentiating them from conditions such as nephritis and transitory gastric disorders.

[20] Jour. Am. Med. Assn., 1915, lxiv, 126.
[21] Arch. f. exper. Path. u. Pharmakol., 1897, xxxviii, 215.
[22] Arch. Int. Med., 1910, v, 61.
[23] Johns Hopkins Hosp. Bull., 1906, xvii, 71.
[24] Loc. cit.

A NEW METHOD FOR DETERMINING THE INTRAGASTRIC TEMPERATURE IN MAN, WITH SOME OBSERVATIONS ON ITS VARIATIONS AFTER INGESTION OF HOT AND COLD LIQUIDS AND DURING DIGESTION.

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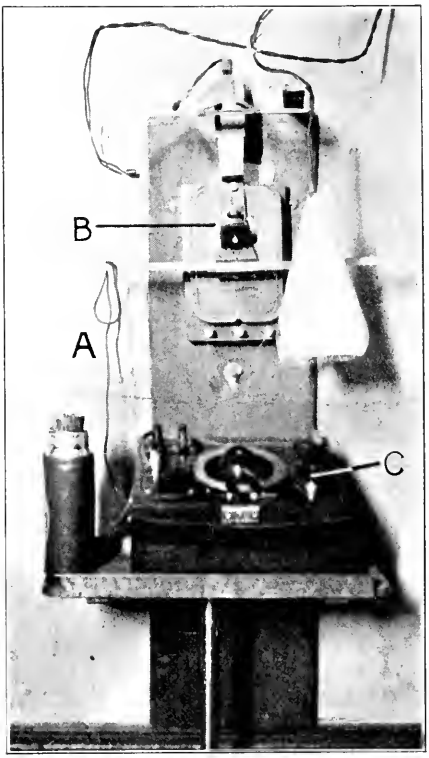
In the Fall of 1914 our attention was attracted to an instrument used by Dr. E. F. Phillips, of the Department of Agriculture, who at the time was investigating the temperature of bee-hives in the Zoölogical Department of the University. This instrument seemed to be especially adaptable to the study of the temperature of internal organs, and consequently we applied it during the next few months to the study of intragastric temperature.

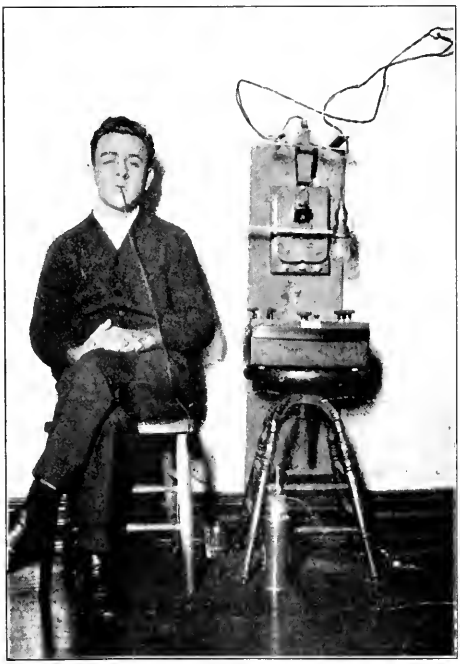
The objects of the experiments we have undertaken were to determine the temperature in the stomach of man during the process of digestion; to test the effects of hot and cold meals; and by comparing the temperature in different parts of the stomach after successive introductions of food and water of varying temperature, to test the correctness of certain views based upon animal experiments regarding the segregation of the stomach contents when separate meals have been taken. In the course of our studies certain other facts came out which may have practical importance.

Previous investigators who have undertaken studies of intragastric temperature seem to have been interested mainly in determining the effect of external applications of heat or cold upon the temperature inside the stomach. Various instruments were employed in these investigations, but most of them were quite crude and did not permit of the determination of rapid changes in the temperature.

D'Hercourt, Chelmonski, Binz, Esmarch, and Schlikoff utilized the mercury thermometer in various forms.

Ewald, the pioneer investigator of stomach temperature, taking advantage of the peculiar ability of a sword swallower, introduced into his stomach a hollow metal tube, through which was inserted a long mercury thermometer, the readings being taken from the protruding end of the instrument. Next he used the Weiderman compass, consisting of a galvanometer and needle, the thermo-element being introduced through a stomach tube. A later and more accurate instrument, that used by Eichler and Schemel, was a resistance thermometer and a registering apparatus consisting of a Deprez d'Arsonval measuring system with a spool and steel magnet. Here also the thermo-element was introduced through a stomach tube.





Photographs illustrating the authors' instrument used in estimating intragastric temperature: *A*, Einhorn duodenal tube containing the thermocouple; *B*, mirror galvanometer; *C*, potentiometer.

The disadvantages of the earlier methods are manifest. The observations were often interrupted and transient; retching and vomiting were frequently provoked by the large size of the instrument introduced, and there was no arrangement by which a meal could be taken with the instrument in position. Thus the satisfactory observation of temperature before, during, and after the introduction of food could not be made.

The apparatus employed in our studies consists of a thermocouple of copper and constantin wires, one pair of ends being placed in a thermos bottle at 0° C. and the other pair being soldered together and run through an Einhorn duodenal tube, at the end of which they were made secure by soldering within the small perforated metal bulb. The thermocouple was then joined to a mirror galvanometer and a potentiometer, the readings being taken in microvolts. This instrument was so calibrated that 40 microvolts corresponded to 1° C., with slight variations at the ends of the scale. Readings could thus be taken within $\frac{1}{40}$° C.

The small caliber of the tubing and of the bulb, which is scarcely larger than a 5-grain capsule, facilitated the ready introduction of the bulb into the stomach and eliminated the tendency to retching and vomiting. The fact that full meals could be taken alongside the tube and that the fluoroscope could be used in locating the position of the metal bulb, thus enabling one to observe variations in temperature between pyloric and fundic areas, are sufficient indications of the advantages of this method.

Comparison of Temperature at the Fundus and Pylorus after Ingestion of Cold Liquid. The bulb was first inserted into the fundus and then into the pylorus of the normal empty stomach and the constant temperature of these regions determined. Next, the bulb being placed in the fundus, the patient was given 120 c.c. of ice water and the temperature recorded; then more of the tube was swallowed, permitting the bulb to work over to the pyloric region, in which portion readings were again taken. Every few minutes, by withdrawing or advancing the bulb, readings were taken at these two areas. The fluoroscope was used in locating the position of the bulb. A short series of practically normal cases revealed the facts shown in the accompanying table:

Showing Comparison of Temperature in the Fundus and the Pyloric Portion of the Stomach after Ingestion of Cold Liquid.

Case.	Temperature before water taken. Fundus.	Pylorus.	Ice-water.	Drop in temperature. Fundus.	Pylorus.	Time to return to normal.
1.	38.0° C.	38.0° C.	120 c.c.	14.2° C.	8.9° C.	20
2.	37.9° C.	37.9° C.	120 c.c.	6.4° C.	5.1° C.	19
3.	37.9° C.	37.0° C.	120 c.c.	8.1° C.	1.2° C.	30
4.	36.9° C.	36.9° C.	120 c.c.	5.2° C.	1.0° C.	31
5.	36.9° C.	36.9° C.	120 c.c.	12.8° C.	8.7° C.	24

1. The prolonged time required for the return to normal temperature, considering the small amount of liquid taken.

2. The marked drop in temperature at the fundus.

3. The striking difference in fundic and pyloric regions. The great difference in temperature of fundus and pylorus after the introduction of cold drinks or ice-cream, as well as the length of time required for the stomach to resume normal temperature, are of special interest in that they confirm, from a different stand-point, the comparatively recent researches of Grützner, Cannon and others.

Physiologists of today consider the fundus a reservoir for retaining the bulk of the food, the more muscular pyloric region being the active motor area. They believe that the material may remain in the fundic region undisturbed for a long time and thus escape mixture with the acid gastric juice, so far, at least, as the interior of the mass is concerned. Grützner after feeding rats differently colored foods and then making sections of the stomachs found that successive portions were arranged in definite strata. Food first taken lay against the walls, while succeeding portions were arranged regularly in the interior in concentric fashion.

Our observations tend to confirm these views, and at least disprove conclusively the old conception that the contents of the stomach are kept in a constant general rotary movement.

Tests Showing the Influence of Hot and Cold Foods upon the Intragastric Temperature. The instrument being in place, a meal consisting of 360 c.c. of ice water with two slices of bread was given to a normal case. At intervals throughout the observation the position of the bulb was alternated between the fundus and pylorus. The greatest drop, *i. e.*, 8.5° C., occurred in the fundic portion, and no less than forty minutes were required for the return to normal temperature at that area. At the pyloric area there was a fall of 4.1° C., which returned to normal somewhat more promptly. Cold milk instead of cold water produced approximately the same results.

Large meals with hot and moderately cold foods mixed showed slight transient fluctuations with the bulb alternating between fundus and pylorus; but when at the end of the meal ice-cream was taken there was a drop of 7.9° C. at the fundus and 3.3° C. at the pylorus, and forty-five minutes were required for the resumption of normal temperature, which occurred at both areas at nearly the same time. When hot coffee was taken after the ice-cream an immediate return to normal temperature was observed.

The accompanying chart illustrates the fluctuations occurring in one instance after the ingestion, in turn, of hot coffee, a full meal, and then after an interval of twenty minutes a glass of ice water. After the water, frequent readings were taken over a period of forty minutes until both fundic and pyloric temperatures had returned to normal. Then after a further period of twenty minutes a moderate

amount of ice-cream was taken, with a resulting pronounced and prolonged fall in the fundic region accompanied by a less marked and shorter drop in the pyloric area.

Chart illustrating the effects of food of varying temperature upon the fundus and pyloric portion of the stomach.

Pyloric Temperature. In observations on the pyloric temperature alone the bulb was introduced into that region and left undisturbed. The bulb was located by the fluoroscope and was found well within the pyloric part of the stomach. An ordinary meal was then given and no change of temperature noted. The taking of ice water just after the meal caused a drop of but 1.2° C. at the pylorus in the course of the next thirty-five minutes.

Observations during Digestion after Elimination of Food Temperature Variations. Next a series of cases was studied with the idea of observing slight changes during digestion, eliminating fluctuations due to the temperature of the test-meal. The bulb having been introduced into the fundus, the patient was given 360 c.c. of milk and two slices of bread heated to body temperature. Oral and rectal controls were taken at frequent intervals. No changes were demonstrable in the intragastric temperature during a period of over one hour in any of the cases observed.

Tests in Abnormal Stomachs. In a few cases of hyperacidity and hypermotility, readings of the temperature were made before and during the gastric digestion to determine if any variations occurred, but the results were negative. One case of this type in which a neurotic element was very marked, and in which there was a great increase in motility, showed no difference in temperature

of fundus from that of pylorus when ice water was taken on an empty stomach.

There was a drop of 5° C. at both areas; the return to normal required twenty-six minutes. Belching and retching continued irregularly throughout the observation, and doubtless aided in the premature mixing of the gastric contents.

Effects of Local Applications. Ice-bags applied over the gastric area produced an average drop of 0.9° to 1° C. in the course of forty-five minutes, while the effects of hot-water bottles applied in the same position were very slight—in fact, almost negligible during three-quarters of an hour.

As has been said, the effects of local applications of heat and cold were the special subject of investigation by former experimenters in this field, and for that reason but few tests were made by us. Our findings confirm those of Chelmonski, Wendrimer and Schutze, Eichler and Schemel[1] and others, who conclude that cold applications to the body surface cause a lowering in temperature of the underlying organs and warm applications affect temperature to a less degree.

We detail only the results of our observations without making any practical deductions at this time. It is obvious that hot and cold foods taken alternately may influence the functions of digestion favorably or otherwise. Extended observation with the aid of the method here used seems to us highly desirable.

AN ASPIRATING BOUGIE FOR THE ESOPHAGUS AND STOMACH.[1]

By Max Einhorn, M.D.,

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In examining patients with digestive disturbances we are occasionally uncertain as to the choice of instrument for the first examination. Generally the stomach tube is used, excepting when we suspect an obstruction along the esophagus. In the latter instance a bougie with an olive-shaped end is employed. Should we find that there is no stenosis, then a second examination with the stomach tube becomes necessary. Even in encountering a resistance with the bougie, it is often desirable to ascertain whether there is fluid or mucus or decomposed tissue in the vicinity of the affected area. To decide this another examination with the stomach tube must be

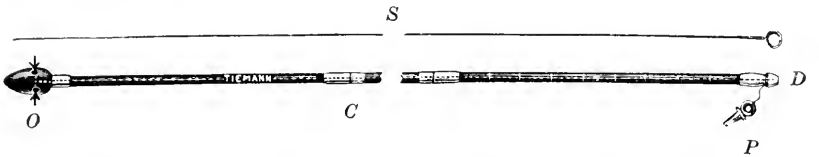
[1] Deutsch. med. Wchnschr., 1911, No. 51.

[1] Demonstrated at the New York Academy of Medicine (Section on Medicine), March 21, 1916.

undertaken. The class of cases under consideration are often in a weakened condition, and any instrumental manipulation on them, even if done with the greatest of care, causes some discomfort.

It appeared to me, therefore, of advantage to construct an instrument which could be used for both purposes at the same time, namely, for the detection of strictures and also for obtaining fluids. The following is a description of the bougie:

The aspirating bougie resembles the usual whale-bone bougie, with the difference that the whale-bone is replaced by a canal-bearing catheter (size 14 F. twenty-four inches long), and that the olives are hollow and perforated in such a manner that fluids can easily be aspirated by a syringe. Different sized olives can be screwed on. The stem is divisible and screwed together in order to be easily handled. A wire stylet or mandrin serves to give the stem the requisite stiffness. A plug is fastened on the distal end. Before withdrawing the instrument the plug is inserted into the distal opening in order to retain any material within the olive for inspection and examination. The drawing illustrates the different parts of the instrument.



The aspirating bougie for esophagus and stomach. *O*, perforated olives of various sizes; *C*, catheter, 14 mm. in circumference and 60 cm. long; *D*, distal end; *P*, plug, attached by thread; *S*, wire stylet.

The same instrument can also be used for obtaining gastric contents in patients who cannot swallow the usual stomach tube, as it can be easily introduced without much assistance on the part of the patient. It can also be employed for fractional tests if desired.

I have used the aspirating bougie, made for me by Messrs. Tiemann & Co., with great satisfaction, and I herewith recommend it to the profession.

THE TREATMENT OF CIRCULATORY FAILURE IN ACUTE INFECTIONS.[1]

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Before we can intelligently combat the symptoms which arise in the course of acute infectious diseases connoting failure of the

[1] Read before the Hospital Graduates' Club, December 23, 1915.

circulation, it is obvious that we should have some understanding of the factors involved in such failure, and if a careful examination of the evidence derived from the experimental laboratory and from the bedside of our patients does not permit us to draw definite conclusions as to what portion of the circulatory mechanism is at fault when such symptoms present themselves, we should at least be prepared to apply our therapeutic efforts in such emergencies with rational empiricism.

In 1899 Romberg and Pässler,[2] in a series of experiments on animals, apparently demonstrated that the collapse observed in various acute infectious diseases was due to paralysis of the vasomotor center in the medulla. They based their belief on their failure to obtain any rise in blood-pressure in asphyxia occurring in pneumonia, diphtheria, septicemia, and other infections after stimulation of the nasal mucous membranes or on stimulation of the central end of the sciatic nerve.

So generally was this work of Romberg and his associates accepted and applied to the human subject suffering from an apparently similar condition, that one will find in nearly all modern theses on the treatment of circulatory failure in acute infections the statement that treatment should be aimed at the vasomotor centers rather than at the heart.

The impulse which served to start the pendulum on its swing away from Romberg's teaching was initiated by Porter[3] and his assistants. They injected animals with a lethal dose of diphtheria toxin, and then, several hours before death would probably have taken place, determined, by the average time of death in control animals, the state of the vasomotor center was tested by measuring the reflex change in blood-pressure obtained by stimulating the depressor and sciatic nerves. Stimulation of the central end of the depressor nerve caused a fall in blood-pressure averaging 36 per cent. of the blood-pressure before such stimulation, while the average rise in blood-pressure obtained after sciatic stimulation was 33 per cent., and they concluded that "the experimental evidence proves that the vasomotor center is not impaired in fatal diphtheria intoxication."

Porter and Newburgh[4] in a series of experiments on animals undertaken to ascertain the state of the vasomotor apparatus in pneumonia, demonstrated "a normal vasomotor reflex with almost wholly consolidated lungs in animals about to die," and they concluded that "experimental evidence proves that the vasomotor center is not impaired in fatal pneumonia."

Romberg and Pässler in their experiments on animals produced fatal pneumonia and diphtheria, and when the animal was near death they massaged the abdomen and caused by this procedure a

[2] Deutsch. Arch. klin. Med., 1899, lxiv, 652.
[3] Am. Jour. Physiol., xxxiii, 431.
[4] Ibid., xxxv, 1.

moderate rise in blood-pressure, and they argued that if the heart muscle was exhausted it would yield to this increase in load and no rise in blood-pressure would follow. That such a conclusion was not justified was shown later by several observers, who proved that massage of the splanchnic area would cause a rise in arterial pressure even in dead animals.

MacCallum[5] injected dogs with diphtheria toxin and found that "though the hearts from poisoned animals are rather weak and apt to be irregular, it is clear that they continue to beat for several hours after they have shown every sign of failure in the body of the dying animal if only the pressure of nutritive fluid be maintained in the coronary arteries . . . all of this seems to show fairly well that the death which occurs in the height of an attack of diphtheria is not exclusively the result of direct injury to the heart, although that may play some part in the process."

Porter and Newburg[6] demonstrated that the heart muscle of a dog which has died of pneumonia contracts as well as the heart muscle from a normal dog, provided the vessel to this muscle is fed with normal blood. They observed that pneumonia blood suddenly fed to a normal heart muscle lowers its efficiency, but that heart muscle gradually exposed to the poison adjusts itself to its poisoned food, and as a result of their experiments they conclude that the heart muscle is not functionally impaired in pneumonia. Clinical observation on the blood-pressure in pneumonia rather supports the experimental evidence produced by Porter that failure of the vasomotor center is at least not always the cause of death in cases which terminate fatally with symptoms of circulatory collapse.

Gibson formulated a rule based upon the pulse-rate and blood-pressure readings in pneumonia which he considered of important prognostic significance in this disease. The rule is that "when the blood-pressure expressed in millimeters of mercury falls below the pulse rate per minute expressed in figures the prognosis is unfavorable."

Newburgh and Minot,[7] however, have demonstrated the fact that the systolic pressure readings in some fatal cases of pneumonia tend to be higher than in those which recover, and in applying Gibson's rule, found that the rule obtained in but 43 per cent. of the cases observed, and they concluded that:

1. The blood-pressure curve does not suggest failure of the vasomotor center in pneumonia.

2. Low systolic pressures are not invariably of evil omen.

3. Blood-pressure measurements cannot be used as a basis for treatment.

There is nothing to justify the assumption that the heart is entirely at fault in the presence of symptoms of circulatory failure

[5] Am. Jour. Med. Sc., cxlvii, 37.
[6] Jour. Exp. Med., xxii, 123.
[7] Arch. Int. Med., xiv, 48.

occurring in the course of acute infections, nor, on the other hand, is there sufficient clinical or positive experimental evidence to permit one to exclude the heart as a factor at least in such failure.

The symptoms which we have been in the habit of ascribing to failure of some portion of the circulatory mechanism in human beings suffering from acute infectious diseases are, briefly: cyanosis; dyspnea; a rapid pulse, rapid out of proportion to the height of the fever; or a pulse-rate which is increasing while the temperature is falling; a sudden fall in blood-pressure; increase in the area of cardiac dullness, especially to the right; a failing first sound at the apex or a diminution in the intensity of the second sound over the pulmonary area; cardiac irregularities; and pulmonary edema.

It has been generally believed that the circulation in the body is maintained chiefly by two factors: the force of the heart as a pump and the peripheral resistance in the vessels maintained by the contraction of the small arteries, which in turn are in a measure controlled by an active vasomotor center in the medulla; but in the light of our present knowledge concerning the integrity of the vasomotor centers in acute infections and in the absence of positive proof that the myocardial efficiency is impaired in such conditions, it seems possible at least that there is a *tertium quid*, a third something, operating outside the heart and vasomotor centers, though more or less intimately associated with them, which controls the flow of blood.

The balance between the circulation and respiration is maintained by conditions existing in the blood. The action of the blood on the respiratory mechanism is not due to CO_2 alone, but also to the presence in the blood of non-volatile acids; and it does not seem probable that one part of the respiratory mechanism, the ventilation of the lungs, is delicately balanced, while the other mechanism, the circulation of the blood, is not so balanced; and Boothby suggests that the factor which regulates respiration and governs the ventilation of the lungs also governs the circulation of the blood.[8] Porter has recently questioned the generally accepted theory that both the vasomotor reflexes and the arterial tonus are controlled by the same center, the vasomotor center, and suggests the possibility of the existence of a vasotonic and vasoreflex center related but separable.[9] Boothby's work suggests the possibility of a combination of a subordinate circulatory center and a ventilation center.

In the rational treatment of a pathological process we must recognize not only the necessity for intelligent management of complications which may arise in the course of such a process, but we must also have a keen appreciation of those procedures which may be instituted in order that such complications may be antici-

[8] Jour. Am. Med. Assn., lxv, 959. [9] Ibid., lxiv, 1659.

pated and possibly prevented. So in a discussion of the treatment of circulatory failure it is necessary to emphasize those factors which are unfavorable to the maintenance of good circulation.

The importance of rest to the patient is perfectly obvious. In the management of any diseased condition, modern therapeutic effort seeks to spare bodily function, and rest in acute infections means circulatory prophylaxis in its very broadest sense. So we select for our patient a comfortable bed that he may obtain the greatest degree of muscular relaxation. We endeavor to relieve his cyanosis, dyspnea, and nervous manifestations by giving him fresh, circulating, and, if possible, cold air. We seek to relieve, by appropriate measures, excessive or unproductive cough, to combat tympanites when it occurs, to relieve excessive pain, and to promote quiet and restful sleep by every means possible. Careful attention to such details constitutes a very important part of the effort we should make to conserve the efficiency of the entire circulatory mechanism.

Tradition must play no part in dictating to our therapeutic judgment in the selection of various drugs by means of which we endeavor to combat the symptoms of circulatory failure when they have occurred, and I say this with a very full appreciation of the necessity for empiricism even in present-day treatment. The drugs which I have chosen to discuss are: alcohol, strychnin, camphor, epinephrin, pituitary extract, the nitrites, and digitalis.

Alcohol. Delafield in his lectures on pneumonia and diphtheria says: "The heart failure is of the same character that we get in any of the severe infectious diseases." . . . "It requires the ordinary management with alcohol and cardiac stimulants."

Janeway[10] says: "Least of all of the so-called stimulants does alcohol deserve the name. It is without influence on blood-pressure or the force of the heart in animals, normal men or diseased conditions."

And these two statements admirably represent the difference, as far as this drug is concerned, between the therapy of twenty years ago and the present-day therapy.

I am loath to discard any of the teachings of that master mind in medicine, Dr. Delafield, for he was a keen observer, and most of the statements made by him years ago hold good for today; but alcohol today is not considered to stimulate any portion of the cardiovascular system—indeed, there is much evidence that it does just the contrary. I am speaking of alcohol now purely from the stand-point of its effect on the circulation. It may do good in relieving active delirium; in fact, I believe that it does; but it is of value here because of its depressant effect on the higher centers already overstimulated by the toxemia of the disease and not

[10] Clinical Study of Blood-pressure, 223.

because it stimulates the circulation. Alcohol causes dilatation of the skin vessels after moderate doses. Large doses cause a fall in blood-pressure; the heart-rate is not changed by therapeutic doses.

Lieb[11] in an effort to determine the reflex effects of alcohol on the circulation found that moderately strong alcohol taken by the mouth produces local irritation of the gastric mucous membrane. Such irritation produces a rise in blood-pressure and an accelerated heart; but if alcohol is given well diluted by the mouth it causes no local irritation, and there is, in consequence, no rise in blood-pressure. Lieb gave cats doses of alcohol varying from 0.5 c.c. to 5 c.c., and in no case was there any change in heart-rate or blood-pressure within half an hour of its administration. He made forty-three observations on twenty-one different patients suffering from various acute infections, typhoid, pneumonia, rheumatism, malaria, etc.

In one patient alcohol was given at a time when circulatory stimulation was called for, yet alcohol not only did not produce any improvement, but, on the contrary, it actually decreased the efficiency of the circulation.

Lieb believes that in the presence of severe toxemia, alcohol loses its power to raise blood-pressure even reflexly. He says: "Advocates of the use of alcohol may claim that alcohol improves the circulation in some fashion other than raising blood-pressure or increasing the heart-rate." It may increase the velocity of the flow or it may improve the efficiency of the heart as a pump; but in applying Tigerstedt's formula $1 \frac{PP \times PR}{SP \times PR'}$, Lieb showed that the changes induced by alcohol in these factors was very slight; in fact, the efficiency of the heart as a pump was decreased.

His conclusions with his experiments as a basis were that "Even though alcohol may raise for a few moments the systolic blood-pressure, and thus act as an apparent circulatory stimulant, it cannot be regarded as a true circulatory stimulant, inasmuch as it decreases cardiac efficiency, raises disproportionately the diastolic-pressure, and lowers pulse-pressure." And in my opinion this statement just about represents the value of alcohol as a cardio-vascular stimulant.

Strychnin is another drug which enjoys a considerable reputation as a circulatory stimulant. Tradition and tradition alone is responsible for its use as such. Vague expressions as to its clinical value, estimated by the feel of the pulse, the subjective improvement of the patient, are frequent in medical literature in this country and to some degree in England. Little is seen in the German and French literature of its use for this purpose. It has never been shown that strychnin does or can relieve cardiac failure. As keen

[11] Jour. Am. Med. Assn., lxiv, 898.

an observer as Mackenzie says of it: "I have carefully sought for its special effect on the heart and found none."

Newburgh[12] in his experiments on patients with this drug shows that "none of the patients were benefited by strychnin; compensation was not improved in the slightest," and he concludes that "neither pharmacological nor clinical evidence justifies the use of strychnin in the treatment of acute or chronic heart failure."

Pilcher and Sollmann[13] show that therapeutic doses of strychnin have no direct effect on the heart. There is no action on the blood-vessels directly. It produces no marked or constant effect on blood-pressure, and they conclude that doses of strychnin large enough to be dangerous (0.05 mg. per kilo) are "usually without action on the vasomotor center, but may stimulate the center moderately."

Parkinson and Rowlands,[14] in England, found no evidence that strychnin used subcutaneously in full doses in cases of cardiac failure produced any change in blood, the blood-pressure, rate of pulse, rate of respiration, or general symptoms within an hour after administration, and concluded that strychnin has no effect which justifies its employment as a cardiac stimulant.

Newburgh[15] showed that strychnin sulphate in medicinal dosage does not increase the output of the heart.

It is, of course, true that the empiric use of drugs is occasionally beneficial; but here is a drug which has been praised as a cardiac stimulant by some observers that fails absolutely to produce results in cardiac failure, and in cases too that responded, after its use, immediately to digitalis in the ordinary manner.

With such weight of evidence against its value, surely we must admit that it is at least a very slender reed to tie to in case of such dire need as often presents itself in the circulatory failure of such diseases as we are discussing.

Camphor has more to recommend it in the circulatory failure of the acute infectious diseases than either alcohol or strychnin, but since I have said that these two drugs are absolutely valueless, I fear that my statement with reference to camphor condemns it with faint praise. Edsall and Means[16] in a series of experiments carried out in human beings to determine the effect of various drugs on the respiration and respiratory metabolism, concluded that "the results obtained with camphor show no constant effect. In one experiment there was a slight fall in CO_2 tension, suggesting that there may have been some stimulation of the center, but in the other experiments there was none. Circulation rate and respiration rate are essentially unaltered."

[12] Am. Jour. Med. Sc., cxlix, 696.
[13] Jour. Pharmacol. and Exp. Ther., vi, 331.
[14] Quart. Jour. Med., vii, 42.
[15] Arch. Int. Med., xv, 458.
[16] Ibid., xiv, 897.

Heard and Brooks[17] in clinical experiments with camphor injected subcutaneously in oil in doses up to 50 grains failed to produce any definite effect.

Plant[18] in his experiments with the effects of camphor on the normal isolated dogs' heart muscle failed to produce any distinct and constant stimulation.

Pilcher and Sollmann[19] in their experimental work with the effects of drugs on the vasomotor center concluded as to camphor that in therapeutic doses it is probably without action on this center.

I am perfectly willing to admit that the centers may be more easily influenced when depressed by disease than when in the normal state.

I have used camphor as a stimulant in acute fevers with symptoms of circulatory failure, and I have thought that it did good, but there are other drugs of much more certain practical and theoretical value.

Epinephrin is fleeting in its action, and in consequence should not be prescribed when sustained effect on the circulatory mechanism is desired. Epinephrin when injected intravenously or intermuscularly causes a prompt rise in blood-pressure, due to the direct action of the drug on the muscles of the vessel wall or on the terminations of the nerves in them.

The heart is at first accelerated and then slowed, the acceleration being due to stimulation of the accelerator fibers in the heart muscle, and the heart, in consequence, contracts more strongly and more completely.

The slowing of the heart is a vagal effect, not direct, but incidental and subsequent to heightened blood-pressure. It has no direct effect on the vasomotor apparatus, but frequently there may be slight stimulation of this center, secondary to the rise in blood-pressure.

Experimental evidence produced by Barbour and Prince[20] shows that epinephrin has the same effect on the coronary vessels of the heart in man as the members of the digitalis group, excepting digitonin—that is, it causes constriction of these vessels.

Epinephrin is, therefore, indicated when there is evidence of acute circulatory collapse with falling blood-pressure and rapid pulse. Janeway,[21] in an article on "The Comparative Value of Cardiac Remedies," says: "I have seen the most amazing restoration from apparent imminent death follow the intravenous injection of epinephrin in large doses; in one case over 4 c.c. of 1 to 1000 solution in a little more than one hour. This was in a case of pneumonia with extreme cyanosis. Life was prolonged for three days."

There is every evidence, experimental and clinical, to warrant

[17] Am. Jour. Med. Sc., cxlv, 238.
[18] Jour. Pharm. and Exp. Ther., v, 571.
[19] Ibid., vi, 345.
[20] Jour. Exp. Med., xxi, 330.
[21] Loc. cit.

the use of epinephrin in acute circulatory collapse occurring during the course of such an acute infection as pneumonia. Indeed, in spite of its fleeting action, one may tide his patient over a circulatory crisis and actually save life by its use.

A word of caution is necessary concerning the age of the preparation of epinephrin to be used. Apparently a product which has been exposed for some time loses its constrictor effect, but not its dilator, and a fall in pressure instead of a rise may take place after the intramuscular or intravenous use of such a preparation.[22]

Pituitary Extract of the infundibular portion of the pituitary gland has an action very similar to that of epinephrin, the difference between the two being rather a matter of intensity than of kind. Blood-pressure is raised, but not so rapidly nor so high as after adrenalin; but the effect lasts for a much longer time. The blood-pressure is raised by direct action on the bloodvessels. Pilcher and Sollmann[23] demonstrated that in animals it had no effect on the vasomotor centers.

The indications for its use are the same as those enumerated under adrenalin, with the addition possibly of its value in the treatment of tympanites when by stimulating the paretic intestinal muscles it often relieves distention, and in consequence the heart is relieved of an important mechanical element favoring failure of the circulation.

The Nitrites, *i. e.*, nitroglycerin, amyl nitrite, and sodium nitrite, have a distinct place in the therapeutic armamentarium of the physician called upon to treat one type at least of cardiovascular failure occasionally seen in acute infections, more often perhaps in lobar pneumonia than in other infections, namely, pulmonary edema.

The nitrites cause direct peripheral depression of the arterioles, with a consequent fall in pressure. The vasomotor center is never depressed in animals by the use of the nitrites. In fact, Pilcher and Sollmann[24] proved that stimulation was the rule. Such stimulation probably is due to the anemia of the centers caused by the dilatation of the peripheral vessels.

Another important observation made by Macht[25] is the effect of the members of this group on excised strips of medium-sized pulmonary arteries. The nitrites caused constriction of the pulmonary strip. This action of the nitrites is corroborated by other experimental data, and the explanation of such action is that the pulmonary artery is richly supplied for the most part with vaso-constrictor nerve terminals. It is this selective action of the nitrite group of drugs which makes them valuable in the treatment of some cases of pulmonary edema.

[22] Jour. Am. Med. Assn., lxiv, 1396.
[23] Jour. Pharm. and Exp. Ther., vi, 405.
[24] Ibid., vi, 323.
[25] Ibid., vi, 13.

CAFFEIN. The effects of caffein on the circulation have been studied both pharmacologically and clinically by several workers during the past two years. Pilcher and Sollmann[26] found in experiments conducted upon animals that caffein caused vasodilatation with sufficient cardiac stimulation to maintain or even somewhat increase blood-pressure.

These actions favor flow, and I shall refer presently to work done by Means and Newburgh to show that it does increase the flow of blood in human beings. This is certainly a highly desirable effect in circulatory disturbance.

Pilcher and Sollmann conclude, as a result of their experiments on animals, that caffein causes: (1) cardiac stimulation; (2) increase in heart rate which is not due to vagus depression; (3) vasodilatation through peripheral depression of the vasoconstrictor mechanism; (4) central vasoconstrictor stimulation is generally ineffectual.

The acceleration in the heart-rate is probably due to direct action of the drug on the heart muscle.

While Edsall and Means,[27] Lucas,[28] and later Newburgh[29] noted little or no effect on blood-pressure, or on the rate or character of the pulse, from caffein administered in therapeutic doses to patients suffering from acute infectious diseases with or without low blood-pressure, Means[30] and Newburgh report an extremely interesting and important series of experiments conducted on human beings in order to determine the effects of caffein on the blood-flow in normal human beings. Their method consisted in determining the rate of absorption of nitrous oxide gas in the lungs. Nitrous oxide gas forms no chemical combination with hemoglobin, but goes into physical solution in blood plasma, so according to a definite coefficient it was possible to calculate how much blood must have passed through the lungs in order to absorb a measured amount of nitrous oxide gas from an original mixture of known concentration.

The blood-flow as determined by this method is, of course, that flowing through the lungs or from right to left heart. There is a marked variation in blood-flow during rest, and this is due to the fact that during rest the supply of blood is "inadequate" to fill the ventricles to their utmost capacity during each diastole; under such circumstances the output of the heart is dependent upon the supply of venous blood and is not directly related to the functional capacity of the heart. During work the flow of blood shows less variation; in other words, "during work the supply of blood to the heart becomes adequate." They showed that during rest or when

[26] Jour. Pharm. and Exp. Ther., iii, 89.
[27] Arch. Int. Med., xiv, 897.
[28] Am. Jour. Dis. Child., vii, 208.
[29] Arch. Int. Med., xv, 458.
[30] Jour. Pharm. and Exp. Ther., vii, 449.

the supply of venous blood is "inadequate," caffein frequently causes a rise in total blood-flow, and often this increase occurs without corresponding rise in pulse-rate. During work no action was obtained from caffein other than an increase in pulse-rate, and consequently there was a slight diminution in systolic output. They suggest in conclusion that during rest or when the flow of blood to the right heart is "inadequate," caffein increases the flow by increasing the venous supply through action on some mechanism outside the heart, when the supply becomes "adequate" or approaches adequacy no such action is obtained.

Digitalis and the other members of this group of drugs is, according to some observers, of little value in the treatment of circulatory failure occurring in the course of acute infectious diseases.

Mackenzie says that "I have never seen much good follow the administration of digitalis in acute febrile conditions;" and again, "Digitalis will be found to be of little value when the heart is already in the grip of some poison, whether it be the specific organism of such diseases as rheumatism, pneumonia, etc., or the toxins of such diseases or such poisons as alcohol."

Gibson says that "In the worst cases of pneumococcal poisoning the heart refuses to respond to digitalis."

Janeway believes that "Digitalis given by the mouth in these cases is worthless." Krehl, on the other hand, believes it to be beneficial.

Just what is meant by the failure of digitalis to act in the presence of fever is not altogether clear. If a reduction in rate is the action expected in this type of case, one can understand why it is said to be of no value. The most decided effects on rate after digitalis administration are noted either in those cases in which the normal pacemaker is eliminated, as in cases of auricular fibrillation, or in those cases with a normally functioning sinoauricular node in the presence of edema.

In view of the work of Cohn[31] in an electrocardiographic study on the action of digitalis it seems probable that slowing the rate of the heart is not at least a "primary function of digitalis." He showed in individuals with a regular rate that digitalis caused a definite lengthening of the conduction time between auricle and ventricle, and also that it produced a distinct "alteration in the size, shape, and direction of the T-wave in the electrocardiogram. These effects were produced in persons with perfectly normal hearts, and even in the absence of any effect on rate. Precisely the same effects were noted in febrile cases, thus proving that whatever its nature the "same sort of support can be given the heart by digitalis during fever as in its absence."

[31] Jour. Am. Med. Assn., lxv, 1527.

In febrile cases showing abnormal rhythm, such as fibrillation and flutter, precisely the same effects on rate were noted after the administration of strophanthin intramuscularly or digitalis by the mouth as obtain in similar conditions occurring in non-febrile states.

Jamieson[32] as a result of his experiments on animals undertaken for the purpose of ascertaining whether the action of a digitalis body when administered to animals suffering from pneumonia differed in its action when no infection or fever was present, concluded:

1. When a like amount of strophanthin is injected intravenously, the mortality is the same in both normal cats and in cats suffering from induced pneumonia.

2. The presence of an acute infection in these animals does not interfere with the action of strophanthin on the heart.

3. The identity of strophanthin action in infected and normal animals renders it probable that a like similarity may be anticipated in man under normal conditions and in pneumonia.

Gunn[33] in his experimental work conducted in animals to demonstrate the influence of temperature on the action of strophanthin on the mammalian heart, showed at least high fever is not the cause of failure of action of digitalis, and that if the heart does not respond to digitalis bodies, it is probable that the heart is in a refractory state from the presence of toxins.

Sollmann, Mendenhall and Stingel[34] agree in the main with Gunn, for they proved that in animals at least ouabain or crystalline strophanthin acts more quickly on the isolated rabbit's heart as the temperature of the animals is raised.

Conclusions. 1. There is neither clinical nor experimental evidence to support the belief that failure of the vasomotor center is the cause of the symptoms of circulatory failure which occur in acute infectious disease.

2. While it has been shown experimentally that the heart is not exhausted in animals dying of acute infectious diseases, there is no positive proof that the myocardium is wholly efficient in its effect to maintain the circulation in the body of the living animal under such circumstances.

3. The hypothesis which suggests the existence of a third center controlling the flow of blood is important even though it is not yet proved.

4. Alcohol and strychnin are absolutely worthless drugs in the treatment of circulatory failure.

5. Epinephrin and pituitary extract are useful in the treatment of sudden circulatory collapse, but their action is not a sustained one.

[32] Jour. Exp. Med., xxii, 629.
[33] Jour. Pharm. and Exp. Ther., vi, 39.
[34] Ibid., vi, 533.

6. The nitrites are valuable additions to our therapeutic armamentarium in the treatment of pulmonary edema under certain circumstances, because of their selective action in constricting the pulmonary arteries.

7. Caffein increases the flow of blood when the supply to the heart is "inadequate," probably by an action on some mechanism outside of the heart.

8. One of the most important contributions of recent times on the action of digitalis is the proof electrocardiographically that it exerts precisely the same effect on the heart in febrile conditions that it exercises in non-febrile states, and whether the rhythm is initiated in the normal pacemaker or not.

REVIEWS

A Manual of Hygiene and Sanitation. By Seneca Egbert, A.M., M.D., Professor of Hygiene, Medico-Chirurgical College, Philadelphia. 6th edition. Pp. 525; 146 illustrations. Philadelphia and New York: Lea & Febiger, 1916.

Although primarily a text-book for students, the chapters devoted to disposal of sewage, industrial and occupational diseases, and to military hygiene are of equal interest to the practitioner.

The introduction, Chapters II, III and IV, on bacteriology, atmosphere, and ventilation and heating, contain nothing new, though the common-sense rules as applied to the last named topic may interest doctors who have suffered by the over-heated and under-ventilated hospitals in which we all must serve.

Chapter V on water supply presents nothing of interest save a quotation from Parkes, who places malaria in the group of water-borne diseases, apparently from ingestion, which is questionable, to say the least.

Chapter VI treats of dietetics in the ordinary way. It is interesting to note in a work published in 1916 that lettuce and celery are classed as "nerve sedatives."

The chapter on industrial hygiene is interesting, but too brief. One expression deserves favorable comment, in a time when many rush to the conclusion that all industrial evils are due to employers, not to employees: in brief, it is emphasized that all the ills to which wage-earners are heir cannot fairly be blamed on occupation, but that some consideration must be given to the personal habits of the individuals outside of work hours.

The subject of military hygiene, treated in Chapter XIV, should be of special interest to the many doctors of today who have enrolled in the Medical Reserve Corps, most of whom are totally ignorant of military training and discipline. The comments on volunteers or militia leaving ordinary civil occupations and plunging into totally different surroundings are quite to the point. This applies equally to those who volunteer in the line or in the medical corps. The author's reference to the Spanish War should be remembered, containing a partial quotation from Dr. Victor C. Vaughan's address to the American Medical Association in 1900: "Camp pollution was the greatest sanitary sin in 1898."

A brief chapter on vital statistics emphasizes the ridiculous incongruity of our system, due to the lack of uniformity in our several States.

The reviewer suggests bad politics as a possible etiological factor in both of the last mentioned abuses. A. G.

The Clinics of John B. Murphy, M.D. Volume V, Nos. 3 and 4. Philadelphia and London: W. B. Saunders Company, 1916.

The June number of the *Clinics* opens with a short talk by Dr. Coffey, in which he advocates the two-stage operation in certain lesions of the gastro-intestinal tract. A large proportion of the volume is devoted to the surgery of the alimentary system, and contains an unusual amount of information in addition to the operative procedure employed in a group of well-selected cases. There is also a group of gynecological cases presented with critical analyses of the history and symptomalology. The editor supplements the text in several instances by statistical reports from Deaver's clinic.

The August number contains more than thirty cases, embracing a great variety of lesions. It is probable that the editor's care to avoid excessive repetition is responsible for recording some of the rarer cases. The reader will be impressed with the remarkable versatility of a surgeon whose work includes such variety. It is worthy of note that there are many appropriate references to the current literature in the recent numbers, as well as frequent references to similar previously published cases which enhance the value of the volume to one who is particularly interested in Murphy's teaching on certain subjects, as for example, ankylosis of the temporomandibular joint which is a feature of this number.

G. M. L.

The Physiological and Pathological Chemistry of Metabolism. By Dr. Otto von Furth, Professor Extraordinary of Applied Chemistry in the University of Vienna; authorized translation by Allen J. Smith, Professor of Pathology and Comparative Pathology in the University of Pennsylvania. Pp. 635. Philadelphia and London: J. B. Lippincott Company, 1916.

The book, containing twenty-five chapters, is based upon a series of as many lectures given to students of biochemistry. Naturally, therefore, it has the advantage of appealing to the larger

number rather than to the more or less limited class of technicians. Its value is perhaps best set forth in the beautifully chosen words of the translator: "The book has for its purpose the presentation of the subject of normal and pathological metabolic chemistry as a broad and connected whole. As a well-prepared and enthusiastic guide, thoroughly conversant with the topography, history, popular activities, spirit, and ambitions of the land through which he is conducting a group of thoughtful travelers, seeks to point out the salient features of the landscape and the accomplishments of the people, their success and their needs, and thus in the end leaves in the minds of the group before him a well-balanced idea of the region, so our author seeks to guide his readers through the living body, following the ingestion of great types of food, their digestion and absorption, pointing out here and there in the unknown field of intermediary metabolism the little which has become known, indicating their resultants, marking the points of departure of disease, presenting the big facts which we know in connection with the metabolic affections, and at all times suggesting the possibilities of further investigation and of orienting our thoughts into conformity with the general plan of nature's chemical performances. The book is thus rather a guide to thought than to the technicalities of the laboratory, and in this appeals alike to students, chemists, biologists, and physicians." There are many page references for those who desire more detailed information upon the subject at hand. Each chapter is divided into subheads, an arrangement which, at the same time, serves to emphasize the importance of the various parts which go to make up the whole and helps the reader to a better understanding of the subject. The book is justly commended as an "orderly and masterful delineation of the important features in the plan of chemical function in the animal economy."

Further than this little more need be said. Credit is due the translator for presenting the subject-matter in so lucid a manner, without attempting to adhere literally to the original text. The German work is widely known and appreciated, so that the present translation should meet with the approval it well merits.

H. D.

A Text-book of Pathology. By W. G. MacCallum, Professor of Pathology in the College of Physicians and Surgeons, Columbia University, New York City. Pp. 1084; 575 illustrations. Philadelphia and London: W. B. Saunders Company, 1916.

Dr. MacCallum has offered in this book his course of lectures at the College of Physicians and Surgeons, presenting the subject

in a philosophical treatise on general pathology from the standpoint of etiology. The various changes in the body are assumed to be due to some form of insult resulting in injuries expressed in various ways, the sequence of events being different in the various organs according to their physical and physiological character. The early part of the book is devoted to alterations in the physical and chemical characters of body fluids and the normal and pathological chemistry of cells and tissues. This is followed by several chapters on tissue reactions to insult and the basis of immunity. Nearly one hundred and fifty pages are then devoted to inflammation and repair. Having established the primary changes of diseased tissues the author then proceeds to detail the effect of various "types of injury" as he denominates them. Great emphasis is laid upon obstruction as a cause of later changes in the organs exposed, as for example the chain of events following stricture of the urethra and lithiasis or the various compensations necessary after failure of the heart in myocarditis or valvulitis.

To bacterial diseases and their effects two hundred pages are devoted, but little attention is given to the biology of bacteria and the properties by which microörganisms become pathogenic. The effects of animal parasites are briefly discussed.

The blood-making organs and the blood are next presented being classified and explained according to the author's classification. These chapters are followed by others on the glands of internal secretions which are presented rather from the standpoint of clinically observed results of hypo- or hyperactivity than from the pathological changes. In the succeeding chapters on the bones great attention is given to clinical changes and chemical alterations are emphasized. Tumors are presented under the old classification of tissue types and the book closes with a general discussion of tumors and what we know about their character viewed as aberrant tissue growths.

As a philosophical presentation of the reactions of body tissue to injury and the basic principles of tissue change the subject is well treated. The clinical side is emphasized, Dr. MacCallum is aware, but he maintains that pathology and clinical medicine are the same thing viewed from different angles. The book seems best suited to teachers in preparing their material, but it is to be feared that undergraduates will be confused by the grouping of numerous examples of tissue change under one heading and will surely miss the systematic grouping of organic changes under organs or systems.

At the end of each chapter several references are given that the reader may find other more elaborate, trustworthy articles.

The illustrations are almost without exception splendid, being well arranged and illustrative of their point. The book is well printed and free from typographical errors. H. F.

Diagnosis and Treatment of Surgical Diseases of the Spinal Cord and its Membranes. By Charles A. Elsberg, M.D. Pp. 321; 158 illustrations. Philadelphia and London: W. B. Saunders Company, 1916.

This is a splendid exposition of the diagnosis of surgical diseases of the spinal cord and its membranes. To begin with the book is very well gotten up on excellent paper and in readable print. Secondly, the reviewer knows of no work which is so freely and so well illustrated as this. Altogether in a book of 321 pages there are 158 illustrations, 3 of them being in colors. Most of the illustrations are from drawings made by that excellent artist Josef Lenhard, and are either of specimens or of active stages of operations. Besides there are a number of studies of patients and roentgen-ray photographs. The illustrations illustrate what the author is talking about and one can readily follow the different stages of a surgical operation with the greatest clearness. One cannot give too much praise to the excellence of this part of the work.

Dr. Elsberg has divided his subject matter in a logical and readable manner. His first division consists in the anatomy and physiology of the spinal cord and a symptomatology of surgical spinal diseases. The second division discusses the operations upon the spinal cord and spinal roots and in the last part there is a discussion of the surgical diseases of the spinal cord and membranes and their treatment. Nothing but praise can be given for the second and third divisions of this book. Dr. Elsberg's skill in spinal surgical operations is so well known that there is hardly any necessity of discussing the good work that has been presented in his book. One might differ with him as to the advisability of operating upon hematomyelia and syringomyelia or in his views regarding the operability of crush injuries of the spinal cord, but no one can find fault with his technic. Perhaps there is so much excellence it is out of place to criticize some phases of this work, yet the reviewer cannot altogether agree with the author in his method of examination of cases, which is hardly complete enough at least from the neurological standpoint, nor with his symptomatology of spinal cord diseases. When one considers, however, that this book is written primarily for the surgeon who is to operate on neurological cases the text is quite sufficient.

There has been a tendency among some surgeons who specialize in nervous work to emphasize the importance of having with their surgical knowledge a certain amount of neurological training sufficient to give them a working knowledge of the usual nervous diseases with which they come in contact. There is no doubt that a surgeon can do much better work when he knows a certain amount of neurology, but the difficulty is that some of these gentlemen are perhaps reaching too far in this direction. It would be not at all

inadvisable to have every neurological surgical case studied by a competent neurologist, for no surgeon if he has any work at all, has the time to give to the neurological side of medicine as much time as the latter deserves. Perhaps if this were done there would be better work and fewer operations. T. H. W.

Obstetrics, Normal and Operative. By George Peaslee Shears, B.S., M.D., Professor of Obstetrics and Attending Obstetrician at the New York Polyclinic Medical School and Hospital; Attending Obstetrician at the New York City Hospital. Pp. 734; 419 illustrations. Philadelphia and London: J. B. Lippincott Company, 1916.

The author has set before us in a pleasing manner the essentials of obstetric theory and practice which he considers will be of most value to student and practitioner. Stripped of all irrelevant matter the text is shorter than in the usual volume on obstetrics, and hence a more easily handled book is obtained. The customary section on embryology has been omitted, as has also that traditional chapter on the development of fetal monstrosities, although sufficient description of these conditions is included in the section on complicated labor to enable the physician to recognize and correctly handle them.

The subject matter is fully abreast of the most recent advances in obstetrics, and while a certain amount of compilation has been necessary, a personal opinion of a moderately conservative nature adds interest to the volume.

The book is divided into four parts: The first part is devoted to normal pregnancy, labor, and the puerperium. The second part takes up the pathology of pregnancy and labor. The third part deals with obstetric surgery, and the fourth and concluding section considers the pathology of the puerperium.

The opening chapters describing the physiology of pregnancy clearly portray the profound changes of the maternal organism. The author lays due stress upon the diagnosis and clinical phenomena of pregnancy, commenting at length upon the scant attention paid to this most important phase of obstetrics, not only in the early stages when the diagnosis of pregnancy must be established, but in the later months when the position of the fetus and its relation to the maternal parts should be determined. The reviewer cannot agree with the statement that the serum diagnosis of pregnancy has a positive value. The rule for the management of pregnancy, labor and the puerperium are excellent. Not a little space is devoted to the subject of anesthesia in labor. In view of the danger to the

child from the morphin-scopolamin method, the author uses an initial dose of the two drugs, followed by a second dose of scopolamin. This he has found to produce a sufficient degree of analgesia in most cases. Should further anesthesia be required, ether is the agent of choice.

The author's views on the etiology of eclampsia are interesting. Nitrogen studies of the blood and excretions have shown a condition of suboxidation to exist in eclampsia. This he believes to be the basis for the symptomatology and pathology; on the strength of his views he has added inhalations of pure oxygen to the treatment of toxemias of pregnancy, not only as a curative but also as a prophylactic. The author believes in the immediate emptying of the uterus for antepartum and intrapartum convulsions.

The pathology of labor is fully considered. There are good chapters on pelvimetry, the diagnosis of fetal positions, and the use of the forceps. The subject of fetal mortality is discussed in some detail. Conservatism is the keynote of the chapter on the treatment of puerperal infection. Hemorrhagic conditions are taken up in an able manner from every standpoint.

The book is full of practical points in obstetrics, the illustrations, many from photographs, are well chosen, and the recapitulation of the more important directions at the end of many chapters is a valuable addition.

The volume which has been published posthumously will be a lasting memorial to the scholarship and high obstetric ideals of its lamented author. P. F. W.

THE PRACTITIONER'S ENCYCLOPEDIA OF MEDICAL TREATMENT. Edited by W. LANGDON BROWN, M.D., F.R.C.P., Assistant Physician to St. Bartholomew's Hospital, and J. KEOGH MURPHY, M.C., F.R.C.S., Surgeon to the Miller General Hospital for South-east London. Pp. 874. London: Oxford University Press, 1915.

NINETY-SIX names are included in the list of contributors to this encyclopedia of medical treatment. These writers are Englishmen of varied repute, and of course the book for this reason has a very decided British atmosphere.

The work is divided into two parts: Part I includes methods of treatment, while Part II is devoted to agents in treatment. In the first part certain general forms of treatment are dealt with, and then the treatment for various disorders is arranged in a systematic way. In the second part are found the classified details concerning the action and use of different drugs.

In their preface the editors state that "despite the many excellent works on treatment that have already appeared, there is still need for

a *Practitioner's Encyclopedia of Medical Treatment* on the lines adopted by the contributors in this work."

The book is too large for easy reference and practical hard use. The binding is weak and the paper is rather coarse. Cheap production has no doubt been the aim of the publishers. A book of this sort must be prepared to meet rough handling. Much of the contents of this volume is the usual material found in such works and does not impress the reader as being the product of an especially thoughtful study of the subject matter at hand. At times remedies are advised which the Council on Pharmacy and Chemistry in this country has not sanctioned. This may not be an objectionable feature, still it hurts the average doctor in this country to have patented medicines suggested for his use. It is disappointing not to find any mention made of the newer ideas in the treatment of diabetes, gastric ulcer, and nephritis as set forth by our own workers.

The work, of course, gives a definite picture of treatment to the man who is in a hurry, and needs to know what he must prescribe. In this, however, it does not differ from a number of American works on the same subject, and indeed it is doubtful whether it serves this purpose quite as well as they do. It is a question whether, on the strength of being new and different, this book has justified its production. It has been issued since the outbreak of the present war, and for this the editors are to be congratulated. T. G. S.

Collected Papers of the Mayo Clinic, Rochester, Minnesota. Edited by Mrs. M. H. Mellish. Vol. VII (1915). Pp. 983; 286 illustrations. Philadelphia and London: W. B. Saunders Company, 1916.

This volume from the Mayo Clinic represents, as usual, the literary output for the current year (1915); it is noted, however, in a "Foreword," that, owing to lack of space, it has not been possible to include all the papers written by members of the Staff during the year: some are represented only by abstracts, and others have had to be postponed until the appearance of the next volume.

One feature about the present volume is new, and is worthy of commendation: this is the fact that the list of contributors, with which the volume opens, shows their status both in the "Mayo Clinic," and on the "Mayo Foundation, Graduate School, University of Minnesota." It was suggested by the reviewer, in commenting on last year's volume, that a lack of knowledge of their status sometimes militated against the statements of certain writers being accepted at what very likely was their true value.

The volume contains, as has been usual of late years, material

representing in fairly well-balanced quantity the various departments of surgery: surgery of the alimentary canal occupies about one-third of the volume, that of the urogenital organs a little over a tenth, that of the ductless glands (including a series of interesting papers on the spleen), and that of the head, trunk, and extremities approximately one-sixth each; while the remaining one-fourth consists of discussions of "technic" and "general papers." Included among the latter are several of Rosenow's weird bacteriological studies.

Although all, or almost all, of the papers in these annual volumes make their appearance elsewhere, and usually in advance of the publication of the Mayo Clinic volume; nevertheless, in their collected form they have come to be so convenient, if not necessary, to students of surgery everywhere that it is a satisfaction to believe that this publication is now established on a permanent basis, and that it will not die when the impetus and direction of the Founders of the Mayo Clinic shall have ceased to be active factors in its preparation; as is not the case, we regret to learn, with the publication from a sister clinic, which after a brilliant but meteoric career, is brought to an untimely end by the lamented death of its talented and indefatigable founder. A. P. C. A.

Medical and Veterinary Entomology. By William B. Herms, University of California. Pp. 350; 228 figures. New York: Macmillan Co.

In this book is found a systematic treatment of insects and other arthropods which may be concerned in causing or in transmitting human or animal diseases. It has not been the intention of the author to produce a comprehensive treatise, but rather a practical manual for the use of students and others immediately interested in the subject. No bibliography is given and references to the literature are not extensive. In Chapters I–V are considered questions of a general character, including insect anatomy and methods of disease causation. Following chapters take up the application of these matters to the various groups of arthropods systematically. The longest treatment is naturally accorded the Diptera, sixty-three pages being devoted to the mosquitoes and one hundred and sixty-six to the flies. There are numerous illustrations, a large proportion of which are reproductions of photographs. Some of these are good but many are unsatisfactory because of harsh lighting, resulting in lack of important detail. The treatment of the subject matter is thorough and clear without too extensive uses of "cases" and their uncritical details. For the convenience of those who wish to familiarize themselves with the

various animals involved there are descriptions, and keys for the larger groups.

A brief statement of the treatment accorded the mosquitoes will serve to give an idea of the character of the book. First there is an account of the systematic position of these insects with emphasis on the characters which differentiate them from similar appearing species. Then follows their life-history and sexual differences. The distinctive characters and behavior of the important species of disease-carrying mosquitoes, together with an extensive key for identifications, closes the chapter. Mosquitoes as disease bearers forms the subject next considered, and here the details of this relation are treated at length. The final chapter dealing with these insects is devoted to practical means for their control, including instances of actual expenditures for various conditions. In a similar way the case of the house fly is taken up at length. While especial emphasis is sometimes placed upon the needs and circumstances of the Pacific coast region the book is one which will make a general appeal and will prove valuable to anyone concerned in the prevention and cure of diseases caused by our insect enemies. McC.

GOULD'S PRACTITIONER'S MEDICAL DICTIONARY. Revised and edited by R. J. E. SCOTT, M.A., B.C.L., M.D., of New York. Third edition. Pp. 962; 70,900 words. Philadelphia: P. Blakiston's Son & Co., 1916.

THE third edition of this dictionary appears with a flexible binding and weighs two and a quarter pounds. The words it contains are those generally used in medicine and the allied sciences. Their definitions are concise and clear. As far as it is possible to say after a brief period of use, these words include among their number all of the terms found in recent medical literature. It is a dictionary at a reasonable price for those who are satisfied with non-detailed word meanings. T. G. S.

THE KINETIC DRIVE; ITS PHENOMENA AND CONTROL. By GEORGE W. CRILE, M.D., Professor of Surgery at the Western Reserve University. Pp. 71; illustrated. Philadelphia and London: W. B. Saunders Company, 1916.

As stated in the prefatory note, "This lecture is in effect an epitome of a monograph in preparation which will offer the complete experimental evidence upon which these themes and postulates are founded." The book represents in printed form the author's 1915

Carpenter lecture before the New York Academy of Medicine; it contains some beautiful photomicrographs, but only stimulates the hope that the promised monograph may soon appear, so that we may know what actual basis there may be for an attitude of dogmatism which, so far as the published evidence goes—we use Dr. Crile's own word—is "unwarranted." J. E. S.

Diagnose and Therapie der Gonorrhoe beim Manne (Diagnosis and Therapy of Gonorrhea in the Male). By Dr. S. Jessner, Sanitätsrat in Königsberg. Second revised edition. Pp. 169. Würzburg: Curt Kabitzsch, 1916.

In this monograph, covering one of the most discussed but least progressed subjects, therapeutically, in genito-urinary diseases, the author has presented a commendable work, of value both to students and practitioners, in which the anatomy of the urethra and its appendages, the symptomatology of gonorrhea and its complications and their respective treatment is detailed.

The critic in his review is conscious of the realization that there is nothing new which might prove useful in the treatment of this disease. Indeed, criticism should be offered that the work, useful as it is only for students and practitioners, not expert in the treatment of gonorrhea and its complications, would be enhanced by the addition of a few illustrations descriptive of the best type of therapeutic armamentarium. Moreover, it should be noted that no mention is made of operative procedures of well-recognized utility and merit, not infrequently necessary in the proper treatment of prostatitis, spermocystitis, epididymitis, etc.

Although biological products play a restricted role in the treatment of gonorrheal affections, they are, nevertheless, of much accessory value both in the pure as well as the mixed chronic complications. The author describes the administration of gonococcic bacterin (Arthigon) in arthritis, but fails to mention antigonococcic serum, an agent of greater potency and value in metastatic or systemic affections, particularly those involving the serous membranes, as synovitis, pleurisy, etc. B. A. T.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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The Volume of Urine in Young Healthy Adults on a Constant Diet.—Addis and Watanabe (*Jour. Biol. Chem.*, 1916, xxvii, 267) have recorded observations on the volume of urine per diem in healthy young adults placed on a constant diet, in which the fluid intake was measured. The authors find that the volume of urine in normal individuals is extremely variable for any single day or part of a day. The average volume of urine when the water intake was 2,070 c.c., varied in twenty individuals from 1,013 to 1,712 c.c. for a twenty-four-hour period, from 684 to 1,195 c.c., for the first twelve hours of the day, and from 501 to 788 c.c. for the first eight hours of the day. The percentage of the twenty-four-hour volume excreted during the twelve hours of the night did not exceed 47 per cent. in any subject.

A Rapid Method for the Diagnosis of Renal Tuberculosis by the Use of the Roentgen-rayed Guinea-pig.—Murphy and Ellis have shown (*Jour. Exp. Med.*, 1914, xx, 397) that white mice which have been exposed to the roentgen rays are much more susceptible to bovine tuberculosis than normal animals, a fact which they attribute to destruction of lymphoid tissue. This observation suggested to Morton (*ibid.*, 1916, xxiv, 419) the use of the roentgen-rayed guinea-pig in the diagnosis of renal tuberculosis, in an attempt to shorten the time required (five weeks) in this well-known method of diagnosis. The author finds that the lymphoid cells of the blood of the guinea-pig can be made largely to disappear from the circulation by a single massive exposure to roentgen rays. "The animal was placed in a pasteboard box of such size that it could not move around and then radiated for a period of ten minutes with the Coolidge tube, the target being twelve inches

distant from the base of the box. A 5 milliampère current was passed through the tube, backing up eight and one-half inches of spark between points. The Snook interrupterless type of machine was employed. No aluminum or leather filters were used." One to two cubic centimeters of urine were injected intraperitoneally, and after ten days the guinea-pigs were killed and examined. Ten patients with renal tuberculosis furnished material for the tests, and it was found possible by means of the roentgen-rayed guinea-pig to secure a positive result in seven to ten days. Apparently, the test works as well when the guinea-pig is exposed to roentgen rays immediately after inoculation. As in normal (unexposed) guinea-pigs the tubercles are most numerous in spleen, mesenteric lymph glands, and liver.

Pancreatic Diabetes in the Dog.—(I) The Influence of Alkali and Acid upon the Glycosuria and Hyperglycemia. Murlin and Kramer (*Jour. Biol. Chem.*, 1916, xxvii, 481) have studied the effect of the administration of alkali and acid on glycosuria and glycemia in depancreatized dogs. They find that sodium bicarbonate and potassium bicarbonate administered by stomach tube may be without immediate effect on the glycosuria and hyperglycemia. A bicarbonate given by mouth to a fasting depancreatized dog may even cause the reappearance of glucose in the urine after it had been starved out. Sodium carbonate (Na_2CO_3) may, on the contrary, reduce the sugar in the urine materially when given by mouth, and when given intravenously, it invariably does so, especially when added to Ringer's or Locke's solution to the amount of about 1 per cent. They furthermore find that the blood sugar does not undergo a compensating increase in percentage, even when the dilution of the blood is accounted for. Dilute hydrochloric acid given by mouth or subcutaneously to the depancreatized dog has, they find, just the opposite effect of alkali—increasing the sugar in the urine without affecting materially the nitrogen elimination—and without causing any effect on the blood sugar. (II) Kramer, Marker, and Murlin (*ibid.*, p. 499), continuing the studies of Murlin and Kramer, have sought to determine the fate of the glucose retained as a result of the feeding of sodium carbonate to depancreatized dogs. They have demonstrated to their own satisfaction that it is not stored as glycogen and that it is not excreted by way of salivary gland, stomach or small intestine. The question whether it is oxidized will be treated in a later communication. (III) Murlin and Kramer (*ibid.*, p. 517) have investigated the influence of alkali on the respiratory metabolism of dogs after partial and total pancreatectomy. In partially depancreatized dogs which still have some capacity to oxidize glucose, the administration of sodium carbonate or sodium hydroxide with glucose is followed by a greater oxidation of glucose than when either is administered alone. Sodium carbonate itself causes but a slight increase in respiratory quotient, or none, whether administered per os or intravenously, to normal or diabetic dogs. Thus it seems that while sodium carbonate and sodium hydroxide alone cannot restore the lost function to an organism completely deprived of its ability to oxidize glucose, either substance can improve the capacity of the organism as a whole to oxidize glucose when this function is more or less crippled, although not completely lost.

SURGERY

UNDER THE CHARGE OF

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Bone Sutures in Granulating Wounds.—SCHMIEDEN (*Zentralbl. f. Chir.*, 1916, xliii, 779) says that he has been practising, in his military service, very extensive resections of joints, in order to avoid amputations in cases of severe joint injuries, with associated soiling of the wound and a wide opening in the overlying tissues. After conservative measures had failed he was able to save limbs by practising a wide opening of the knee-joint. All the ligaments were divided and the joint opened as for an excision. If the ends of the bones are fragmented, and secretions are retained in pockets between the fragments, an excision of the infected portions must be done. After the opening is made, the limb is kept in the flexed position by a bandage and soon afterward an extension apparatus is applied to keep the wound open. This treatment permits the wound to gradually clean itself. When this occurs and the fever disappears, the defect is opened up widely under lumbar anesthesia without regard to the discharge from the wound. Both bone stumps are separated by division through the granulation tissue and the ends sawed off smoothly. Holes are bored through to fix them firmly together. No effort is made to adapt or suture the soft tissue part of the wound. The whole limb is fixed in a plaster cast from the pelvis to the toes. An opening involving three-quarters of the circumference is left and is bridged over by metal splints. The discharge is taken care of by frequent dressings. In six to eight weeks enough bony union is usually obtained to permit the application of a second cast, which is often the last. The wire sutures may be removed in four to five weeks after operation, through the cast opening. The advantage of this method of treatment lies in the rapidity and certainty of healing, with very little loss in the length of the limb.

The Osteoplastic Activity of the Periosteum.—VOGEL (*Zentralbl. f. Chir.*, 1916, xliii, 794) reports the case of a five-year-old girl at the time of operation, in November, 1906, for a marked curvature of the left tibia from rickets. Notwithstanding the occurrence of primary healing, union of the bone did not take place. Passive hyperemia and repeated subperiosteal blood injections by the Bier method were also without success. December 19, 1907, the bone ends were united by wire sutures. Primary union without consolidation of the bone again resulted. May 8, 1908, the site of non-union was freely exposed, the periosteum elevated on the proximal and distal sides, the wire suture and all infragmentary callus removed, and on both sides of the tibia a plate of paraffin, $2\frac{1}{2}$ cm. long, $1\frac{1}{2}$ cm. wide, and 2 mm. thick, was so

placed under the periosteum, that the space between the bone ends was bridged over. The wound was closed and a fixation dressing applied and primary union resulted. After three months there was a certain degree of but not absolute union. Vogel did not see the child again until the autumn of 1915. The previously treated tibia was then firmly united, but at the site of operation, it was bent into the varus position with massive bone thickening. On January 1, 1916, the curve of the tibia was again corrected, this time by a wedge-shaped osteotomy. The following conditions were found: At the highest point of the bone thickening, between the callus and the overlying periosteum, lay the two pieces of paraffin, unchanged since they were depositited there eight years before. They were entirely loose, not adherent to the periosteum or bone, and were readily pulled out by forceps. The paraffin, carefully dissolved, showed by the microscope, no foci of organization. It was exactly like a control piece of paraffin. Vogel says that the paraffin, by putting the periosteum under tension (as by the Bier subperiosteal blood injections) excited the periosteum to callus formation.

A Contribution to the Operative Treatment of Forearm Synostosis (Fracture-Callus).—Schlapfer (*Deutsch. Ztschr. f. Chir.*, 1916, cxxxii, 225) discusses the subject of synostosis between the radius and ulna, acquired and congenital, based upon the results of two operations on one case. The first operation, performed ten minutes after the accident, was unsuccessful, the callus bridge between the radius and ulna was chiselled through in its whole length, after which the supination of the forearm was complete, it having been fixed in pronation from the accident to the time of this operation. Nearly two years later there was no pronation of the forearm and the roentgen ray showed that the callus union of the two bones had reformed. A second operation was then done. With hammer and chisel the callus was so freely removed that the forms of the two bones were restored to the normal. The radius was then wrapped in a fat-fascia flap taken from the thigh, which was fixed in position by catgut sutures. The muscles were sutured by catgut, the subcutaneous tissue and skin also being sutured. After the operation, pronation and supination were rather free. Primary healing occurred. Passive movements were begun on the third day. When the patient was discharged, seventy-two days after operation, there was no active pronation or supination but, passively, these movements were possible to about 25 degrees. The roentgen ray showed normal configuration of both bones. A few bone splinters left in the soft tissues were in the process of absorption.

The Surgical Uses of Ozone.—Stoker (*Lancet*, October 21, 1916, p. 712) says that the first 21 cases treated by oxone at the Queen Alexandria Military Hospital cannot be regarded as anything but satisfactory from every standpoint, humanitarian, scientific, or economic. The cases were, for the most part, those of cavities and sinuses in the femur and tibia. It is the experience of those who have seen a great deal of war surgery that such cases obstinately resist treatment and are apt to remain unhealed for months and years. The treatment consists of the application of ozone to the affected parts; it is, there-

fore, necessary to have an apparatus for generating ozone which shall be portable and easily worked. Stoker uses the Andriolis ozonizer. It is called into operation by a four volt battery animating a $\frac{1}{4}$-inch sparking Rhumkorff coil. The oxygen passes from a cylinder through the ozoniser, and in doing so comes in contact with a metal armature, the effect of this being to transform the oxygen into ozone. A tabulated statement showing the effects of the treatment in 21 cases with chronic bone sinuses is very favorable to this method. The properties of ozone are, are far as one can say at present, three: It is a strong stimulant and determines an increased flow of blood to the affected part. It is a germicide, which destroys all hostile microörganic growth. As the French chemist, Hennocque, has shown, it has great powers in the formation of oxyhemoglobin. The ozone is applied on the wounded surface or to the cavities and sinuses for a maximum time of fifteen minutes, or until the surface becomes glazed. Ozone has the particular power of disclosing dead bone, foreign bodies, septic deposits, etc. Stoker believes it does this by destroying the granulations and micro-organic growths (presumably unhealthy) that are found in close contact with septic deposits, foreign bodies, or dead bone. Wounds and sinuses, etc., are washed twice daily with boiled water and a dressing of dry gauze is applied. It must be observed that at first ozone causes an increase of the discharge of pus; later on the pus is replaced by clear serum, which at a still later stage becomes colored reddish or pinkish. In open wounds it is necessary to strip off the parchment-like film surrounding the edges, which is composed of oxydized serum. This is easily effected by applying a hot compress for fifteen or twenty minutes, after which the film can be easily peeled off with a dissecting forceps.

THERAPEUTICS

UNDER THE CHARGE OF

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Autogenous Defibrinated Blood in the Treatment of Bronchial Asthma.—Kuhn and Emsheimer (*Arch. Int. Med.*, 1916, xviii, 445) say that inasmuch as bronchial asthma is due to sensitization by a foreign protein, immunization by injection of the causal protein should be of benefit. They believe that with each attack of asthma there occurs a sudden or gradual liberation into the circulating blood of the protein which excites the attack. If blood is withdrawn during the attack it presumably contains the toxic protein or antigen. Repeated injections of this defribrinated blood are made subcutaneously at varying intervals. The quantities of antigen contained in each injection are so minute as to create a very small amount of antibody each time,

and never to result in an attack. Thus the tolerance of the body for the protein may be enhanced. Naturally in an ideal course of treatment it would be desirable to obtain the blood each time just prior to or early during an attack of asthma, since it is assumed that it is time that the antigen is in the circulation in the greatest amount. It is possible that the benefit from the treatment may rest on an empirical basis. It can be contended that the mere withdrawal of blood from the circulation and its reintroduction subcutaneously is not sufficient to produce a marked biologic effect on the involuntary muscles. It may also be said that the original presence of antigen in the circulation should also serve to immunize the individual. But this does not take place in asthma, whereas the clinical results from the treatment would seem to permit of the foregoing interpretation. The authors state that six successive patients with bronchial asthma, treated by repeated injections of autogenous defibrinated blood, have shown definite improvement as indicated by diminution in frequency and severity of attacks, gain in weight, increased ability to work and improved subjective symptoms. The results in these cases are promising enough to justify a continuation of the treatment and to find in what proportion of the cases it is of benefit, and to what degree.

A Study of Serum Salvarsanized in Vitro.—Swift (*Jour. Exper. Med.*, 1916, xxiv, 373) says that, following the introduction of intraspinal injection of serum in the treatment of patients with syphilis of the central nervous system, numerous workers have attempted to inject intraspinally salvarsan or neosalvarsan in weak dilution. When more than 1 mg. has been repeatedly injected, several observers have noted symptoms of myelitis in the lower segment of the cord. Marinesco and Minea have observed that neosalvarsan diluted with serum is less irritating than when diluted with normal sodium chloride solution. Fordyce and Ogilvie advise that only a fraction of a milligram of salvarsan be mixed with the serum for intraspinal injection. Clinical evidence seems, therefore, to indicate that only small amounts of salvarsan or neosalvarsan can be safely injected into the subdural space. The main objection to subdural therapy of cerebrospinal syphilis has been that the serum injected contained such small amounts of salvarsan. Obviously it is necessary to keep the amount of any therapeutic agent below the injurious dose. Therefore, with the evidence at hand only small amounts of the drugs at our disposal can be used. The object then must be to use them in the least injurious and most potent form. From the evidence brought forward by Swift this would be the addition of small amounts of salvarsan or neosalvarsan to the serum of salvarsan-treated patients. This serum should be allowed, preferably, to remain in contact with the clot overnight, and should be heated after the addition of the salvarsan. Although this technic is complicated it could be easily carried out in clinics where large numbers of patients are treated, or if the salvarsan is procurable in ampules containing small amounts so that dilutions for addition of the drug to the serum might be economically prepared. Swift summarizes his study as follows: addition of salvarsan to serum *in vitro* produces a spirocheticidal mixture which is increased in potency by heating. The heated serum of salvarsan-treated patients is more spirocheticidal if it has been in contact with the

clot overnight than if it has been separated immediately after coagulation. This is not true with the serum from blood which has been salvarsanized *in vitro*. The addition of salvarsan directly to serum produces a more potent mixture than results from the serum from blood to which salvarsan has been added in equivalent amounts. The increase in activity of salvarsanized serum produced by heating to 56° C. is due in part to the removal of inhibitory substances in the serum and in part to a direct increase in spirocheticidal power in the heated salvarsan. Both salvarsanized and neosalvarsanized serum are rendered more spirocheticidal by heating. A more active spirocheticidal mixture is produced by mixing small amounts of salvarsan with the serum of a salvarsan-treated patient than with normal serum.

Immune Human Serum in the Treatment of Acute Poliomyelitis.—Wells (*Jour. Am. Med. Assn.*, 1916, lxvii, 1211) says that the administration of immune serum in acute poliomyelitis is based on recognized principles of immunity. Because the lesions are not confined to the nervous system and because the lesions therein consist essentially of perivascular infiltration, intravenous injection of serum appears to be a rational procedure, either alone or in combination with intraspinal injection. Intravenous injections of serum should, if possible, consist of doses of from 50 to 100 c.c. or more daily. Following intravenous or intramuscular injections of serum, spinal fluid should be withdrawn. Intraspinal injections of serum usually produces an increase in the number of the leukocytes with increase in the proportion of polymorphonuclear cells in the spinal fluid. In the fifteen cases that Wells treated no ill effects followed the use of serum, either by intravenous or intraspinal injection. In all cases, after intravenous injection, and to a less degree after intraspinal injection, a noticeable improvement usually occurred, which, unfortunately, however, in some cases was only transient. Early administration of the serum is urged, necessitating therefore an early diagnosis of the disease; in severe cases late administration of the serum has produced little if any noticeable influence on the course.

The Action of Benzol.—Weis Rotten, Schwartz and Steensland (*Jour. Med. Research*, 1916, xxxv, 63), in a previous communication, reported experimental work on the action of benzol by giving rabbits two or more daily subcutaneous injections of equal parts of olive oil and benzol. It was found that in all cases in which the animals survived the primary fall in the leukocyte curve there followed a primary rise which reached a normal level and in many instances reached the original level. This primary rise was always independently of any further injections, followed by a secondary fall, which in turn was followed by a secondary rise to a normal level. In the secondary fall the leukocyte curve almost invariably reached a level nearly as low as the primary fall, and in some instances even lower. Further work has given similar results. The authors' experience indicates that the mortality during the secondary fall is practically as great as during the primary fall. In all animals surviving the secondary fall there occurred a return of the leukocyte curve to a normal level, and there was no evidence of any subsequent falls. As a descriptive term appropriate for indicating

the occurrence of the two periods of leukopenia above described Southard has suggested the term "diphasic leukopenia." For the first period, the authors suggest the term "Protophase," this extends from the onset of the primary fall and ends with the termination of the primary rise. The second period denoted "Deuterophase," extends from the onset of the secondary fall and ends with the termination of the secondary rise. The authors found this latter phase, following subsequent sets of subcutaneous injections of equal parts of olive oil and benzol in rabbits the same in every respect as that following a first set of injections.

Syphilis of the Nervous System.—Fordyce (*Med. Rec.*, 1916, p. 575) in outlining the course to be pursued in the treatment of syphilis of the nervous system considers that the best procedure is to give provocative injections of salvarsan to patients with a negative blood and a positive spinal fluid, and take the Wassermann at stated intervals. If the Wassermann remains negative, subarachnoid treatments may be begun at once. When both blood and spinal fluid are positive, two or more injections of mercury should precede the intravenous administration of salvarsan and after two or three doses of the latter the intraspinal treatments are begun, supplemented by intravenous injections. In paresis, intraspinal injections are best begun after the first intravenous treatment, while the intervals between doses are regulated by the patient's reaction. Where subdural injections are well borne, they may be given in a series of four to six, one or two weeks apart with a rest period of four to six weeks before giving another course. Ogilvie's modification of salvarsanized serum is now used by Fordyce, in which method salvarsan is added directly to the blood serum. Blood serum removed indifferently from patients acts as well as autogenous serum, and the most important step in the technic, next to absolute asepsis, is the use of a nearly neutral salvarsan solution. The blood is removed from an arm vein and centrifugalized to secure complete removal of red cells. To 8 or 10 c.c. of this serum 0.05 to 0.5 mgm. of salvarsan is added and the mixture is incubated at 37° C. for thirty minutes. General paresis patients tolerate larger doses than those with tabes or other forms of cerebrospinal syphilis. The initial dose for tabetics should be 0.05 to 0.1 mgm., depending on the bladder involvement and the amount of pain present, and the quantity is gradually increased up to 0.2 to 0.3 mgm., if the patient will tolerate it. Activation of the lesions after the first injection is not a contra-indication, but calls for care. There seems to be no limit to the number of injections that can be given. Cure, amelioration or failure is dependent upon the extent and type of the morbid process. Success depends largely upon whether the morbid process is an active meningeal inflammation or a degeneration of essential nerve structures. Active inflammation with a strongly positive fluid gives a hopeful outlook, while degeneration with atrophy and sclerosis, with negative or weakly positive fluid, does not present so encouraging a prognosis. In his conclusions Fordyce states that all patients at the end of the first year of their infection should have a spinal puncture, whether or not they have any signs of the disease. If the fluid is negative to all tests, they may be assured that there is little danger of later development, whereas a positive

colloidal gold test with persistent Wassermann in high dilutions points to an impending paresis. In the great majority of patients there is little risk attending either intravenous or intraspinal treatment. In diseases of the central nervous system it is not altogether a harmless procedure according to Fordyce and it cannot be emphasized either too strongly or too frequently that every precaution be carefully carried out in regard to preparation, size of dose and sufficient rest in bed after treatment.

The Indications for Splenectomy in Certain Chronic Blood Disorders.—Balfour (*Jour. Am. Med. Assn.*, 1916, lxvii, 790) says that the success of splenectomy in splenic anemia, with associated splenomegaly and severe anemia, has led to splenectomy in other diseases in which splenomegaly and anemia are characteristics. One of the most interesting of these is the syphilitic spleen; good results have followed splenectomy in three cases of this form of syphilis. All the patients had gummas in the liver, and in the spleens removed the spirochete could be demonstrated in large numbers. It was also a clinical observation that although the virulence of the infection could be more or less controlled by antisyphilitic treatment, it was not eradicated. From the foregoing facts, the conclusion may be drawn that the spleen picks up the spirochetes and harbors them, and this conclusion is supported by the surgical observation that removal of the spleen, followed by antisyphilitic treatment, results in prompt and permanent relief. The remarkable results following splenectomy in splenic anemia and hemolytic jaundice, particularly the latter, appear to have provided the basis on which Eppinger and others have suggested that similar surgical treatment might prove of value in pernicious anemia. Balfour believes that splenectomy should be considered in every case of pernicious anemia in which the diagnosis has been established and all possible etiologic factors which might be independently remedied have been excluded. The failure of other means to combat the disease, the previous fatal prognosis, and the low operative mortality are strong arguments in favor of splenectomy. The activity of the disease is an important consideration in discussing the advisability of operation. Splenectomy should be undertaken with hesitation in acute stages of pernicious anemia and especially with a falling blood picture. The operation cannot at the present time be advocated when cord changes and other permanent pathologic processes mark the terminal stages of the disease. Moreover, as already suggested, if it is not feasible to tide a patient over the critical periods by transfusion, splenectomy is contraindicated. Definite statements based on the qualitative blood picture cannot be made, but if the hemoglobin is under 25 per cent. and cannot be raised, operative treatment is of considerable risk and has doubtful results. The extent of the disability of the patient must of course be carefully considered. If a patient with every evidence of the disease is able to carry on his usual occupation, splenectomy cannot be strongly advocated, yet these may be the very patients in whom best results may be obtained. The operation may be urged more legitimately when the patient is unable to do his work or is a chronic invalid.

PEDIATRICS

UNDER THE CHARGE OF

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Fainting Attacks in Children.—Hutchinson (*Brit. Jour. Child. Dis.*, 1916, xii, 161) reports a study of ten cases of fainting attacks in children in an out-patient clinic. It was noticed that both sexes suffer from the attacks but girls rather more frequently than boys. Occasionally they date from early life but usually do not appear until the fifth year or later and are commonest after school age. In general features the attacks are similar in all cases. The child is observed to "go white" and may fall down but does not lose consciousness entirely although it is often dazed or even only semiconscious. Occasionally vomiting or retching occurs but in no case was urine voided involuntarily. Attacks last from a few minutes to half a hour and pass off gradually often followed by a headache. The commonest time for the attacks to occur seemed to be before breakfast or while the child was getting ready for school. Of the children examined many were nervous and dyspeptic but in a considerable number the general health was quite good and the appearance flourishing. There seemed to be no relation between the attacks and any previous disease. The author observed one attack in a boy he was examining. The boy became pale and giddy, the pulse slow and feeble, the heart sounds toneless. He was quite conscious but somewhat confused and revived gradually after lying down. Hutchinson could discover no cause for the susceptibility of these attacks, but over-strain at school seems to play a part in some cases. There is no evidence that the heart is primarily responsible and the origin is probably a nervous one primarily. Change of air to the seaside, removal from school, strychnin as a tonic and attention to digestive organs include the treatment which usually clears up the attacks speedily.

Meningitis in the Newborn and in Infants under Three Months of Age.—Koplik (*Arch. Pediat.*, 1916, xxxiii, 481) in discussing meningitis in the newborn says that this condition is often overlooked at first because the nervous and physical reaction to irritation in the newborn is extremely slow and obscure. Many cases of primary meningitis are only suspected as such after developing sufficiently to give signs of cerebral pressure. In the newborn even with cerebral symptoms the body remains limp. The symptoms most characteristic of meningitis in the newborn are, convulsions, repeated at first and, if recurring, as is rather characteristic, do so two to four days after birth. Convulsions are accompanied by rather high fever, dropping gradually and after the first week often running but one or two degrees above normal. Periods of constant crying and restlessness with normal condition of the bowels is characteristic. The fontanel may show

bulging only days or weeks after the onset, giving at first no clue. Before fluid accumulates there is no MacEwen sign. Kernig's sign is usually absent as is Brudzinski's sign and cannot be elicited until a much later period. Rigidity of the neck is elicited at first rarely, or not at all, until weeks postpartum. Very characteristic of purulent cases are convulsions accompanied by a fall in temperature and symptoms of collapse with cyanosis resembling chills. Constant vomiting in the form of regurgitation irrespective of feeding time is characteristic, as is a peculiar groaning noise made in breathing. The temperature may, after a week, drop to normal and stay there. Tetany is of even rarer occurrence than meningitis while in meningeal hemorrhage from pressure there is no fever, and cyanosis and respiratory signs would be present. Even a suspicion of meningitis would indicate lumbar puncture.

Creolin in Scabies in the Infant.—MONTGOMERY (*Arch. Pediat.*, 1916, xxxiii, 525) recommends creolin as an effective innocuous antiseptic which is an admirable non-irritating parasiticide adaptable to the treatment of scabies in the infant. Scabies in the infant tends to spread all over the body and at this age is frequently associated with eczema and pyogenic skin infection. Sulphur, while probably the best remedy for scabies, is highly irritating to some skins and often very irritating to the sensitive skin of the infant. Balsam of Peru is an excellent remedy but difficult to obtain absolutely pure, while betanaphthol as a salve is a fine antiscabetic, but unfortunately in several instances has caused death when employed for scabies. Creolin, however, offers the best substitute for sulphur which sometimes leaves an irritation of the skin long after the scabetic condition has subsided. The following prescription is given, being the formula used by Dr. Werther of Dresden. ℞ creolin, 10.00; sapo viridis, 30.00; adipis benzoati ad. 100.00. M.—Sig. Rub in once a day. The green soap adds to the penetrating qualities of the preparation but it is not a necessary ingredient and may be undesirable as drying and irritating to the tender infant skin.

A Clinical Study of Postnasal Infections.—BAXTER (*Arch. Pediat.*, 1916, xxxiii, 729) made a study of 60 cases of postnasal infections occurring during an epidemic in 1915. Five of the cases were complicated by acute hemorrhagic nephritis. Only 3 cases of this series were complicated by an acute tonsillitis. The cases range in age from one to eight years. The diagnosis of postnasal infection was made from the presence of constitutional symptoms of an infectious condition supplemented by negative physical findings in all parts of the body except on the part of the nasal passages. The symptoms were either a mild coryza or obstruction to nasal breathing with the anterior nares free and a mucopurulent discharge from the postnasal space. In some cases there was adenitis of the lymphatic glands behind the sternomastoid muscle which drain the postnasal space. There was no glandular suppuration in any of the cases. The duration of the infection, exclusive of complications was from one to three weeks. No complications on the part of the heart were observed. Five of the cases were complicated by acute hemorrhagic nephritis. This occurred mostly in the

older children of from four to eight years. There was involvement of the middle ear in more than 75 per cent. of the cases, and this was especially frequent in infants under two years. The cases studied bacteriologically did not show the prevalence of the streptococcus, but usually showed a pure culture of staphylococcus. In involvement of the middle ear it is important not to be hasty in doing a paracentesis, especially in infants under two years. In the present series the results obtained without paracentesis were practically as good as those where a paracentesis was done. It is not good treatment to do a paracentesis in every case of otitis media. Besides general treatment the author employs the following: Irrigation of the ear, when involved, with a warm solution of boric acid or carbonate of soda two or three times in twenty-four hours. Two per cent. carbolic acid in glycerin instilled into the ear at intervals of three hours. Irrigation of the nasal passages with warm alkaline solution under gravity pressure twice a day. The cases of nephritis were given the usual treatment for this condition. Fisher's solution was used per rectum by the drop method and instillation in 4 cases. The immediate recovery occurred in about four weeks and the ultimate clearing up of the urine in from two to four months.

OBSTETRICS

UNDER THE CHARGE OF

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Biochemical Function of the Decidua.—Gentili (*Annali di ostetricia*, No. 2, 1916) has studied the biochemical functions of the decidua with special regard to the formation of lipoid material. The article is accompanied by microscopic illustrations showing the alteration in cells in various conditions of disturbed metabolism. His researches show that under certain conditions the decidua may contain a considerable proportion of lipoid bodies without passing into a state of actual fatty degeneration.

Backward Displacement of the Pregnant Uterus.—In an article upon this topic in general, McCann (*Brit. Med. Jour.*, July 1, 1916) states that when the pregnant uterus is displaced backward it will sometimes return to the normal position. To secure this result without interference the patient must be kept at rest in bed and the catheter used regularly. Retention of urine is one of the most frequent of the conditions, and one of its most serious complications. In making efforts to replace the uterus the greatest gentleness must be employed, as such efforts frequently result in abortion. When the pregnant uterus is fixed backward by adhesions it may be necessary to open the abdomen and free the adhesions. In two cases treated, one patient went

to term and was successfully delivered, the other aborted four weeks after operation. If other methods be thoroughly used operation will rarely be necessary. In the experience of the reviewer rest in bed and the use of the catheter may to advantage be supplemented by having the patient take the knee-chest posture night and morning. Attendance of a nurse is very desirable, and she should see that when the patient takes the knee-chest posture air enters the vagina freely. To secure this the parts should be separated by the nurse, or a medium-sized cylindrical rubber speculum should be inserted. Where the uterus does not go back readily but is mobile, tampons of carded wool run out of 0.5 per cent. lysol solution have been found useful.

The Abderhalden Test for Pregnancy.—In Bossi's clinic at Genoa, CARLINI (*Annali di Ostetricia*, No. 3, 1916) has tested the Abderhalden method by dialysis and by the method of color estimation. He finds, as have many others, that the method of dialysis frequently gives the positive result where there has been no pregnancy, and especially in diseases of the uterus and ovaries. In the method which uses the estimation of color he could come to no definite positive conclusion. In general his results coincide with those of others, that even with the most careful technic the reaction is of very limited application.

Pelvimetry during Pregnancy.—PONZIO (*Annali di ostetricia*, No. 3, 1916) has studied the examination of the pelvis during pregnancy by the use of the roentgen ray. He illustrates his method by a picture of the pelvis viewed by the fluoroscope, and illustrates a method of computation for estimating the true conjugate; also the distance between the pubes and the coccyx. He refers to the work of Manges, and his conclusions and method. To those who are practising the use of the roentgen ray for diagnosticating purposes, this paper will be of value.

Surgical Replacement of the Retroposed Uterus.—BISSELL (*Am. Jour. Obst.*, July, 1916) describes his method of permanently curing backward displacement of the uterus, and gives the results of pregnancy and labor subsequent to the operation. His present method consists in grasping the round ligament near its center with two instruments 2 cm. or more apart. Gentle traction is made, and the tense portion of the ligament between the forceps is split through its middle longitudinally, the point of the knife passing down between the surface of the broad ligament. Each split portion of the round ligament is now grasped with forceps, and the other instruments released. Straight scissors are next passed through the split in the round ligament and forced down between the layers of the broad ligament, and opened several times to separate the surfaces, and with the same scissors the longitudinal division of the round ligament is continued on the distal side to within close proximity of the infundibuliform process of the ligament, and on the proximal side to its uterine insertion. The anterior split portion of the round ligament is now severed about 1.5 cm. from the infundibuliform process, and cut away from its broad ligament attachment. The posterior split portion is severed about 1.5 cm. from its uterine insertion, and cut away from its broad ligament

attachment. The cut end of each remaining split portion of the round ligament is sutured to its corresponding cut end with silk or linen, and the apposing lateral surfaces of the split portions are held together by fine catgut at their middle. The round ligaments are thus shortened about 2.5 cm., and larger than previously in diameter. The middle of the posterior surfaces of the broad ligament is now folded on itself and penetrated at its base with a suture of chromic gut, avoiding the Fallopian tube. When this suture is tied the posterior surface of the broad ligament is narrow, and the cut edge of the fold united by continuous catgut suture. The same thing is done on the anterior surface of the broad ligament, avoiding the uterine artery. This narrows the entire ligament. The combined effect of shortening the round ligaments, and narrowing the broad ligaments brings the uterus into its normal anterior position. When the uterus is unusually large and heavy a temporary suspension by chromic catgut is added to this portion. He has studied the results of this in 185 cases. In all there were 8 failures so far as the position of the uterus was concerned. In 7 cases he has had the opportunity of reopening the abdomen. In one of these patients the abdomen was opened more than seven years after the original operation, and adhesions found between the uterus, bladder, and anterior surface of the broad ligament. At the second operation the uterus and adnexæ were removed. After the operation the patient had given successful birth to three children. Fourteen women in this series have passed through labor in such operation, and 19 births have occurred. In 1 the uterus again became displaced backward; in 3 forceps were used; in 1 vaginal Cesarean section performed. One of the patients after operation for displacement had labor followed by complete prolapse, for which hysterectomy was finally done. One case aborted at the third month. The majority of testimony obtained by the clinical investigation of these cases is in favor of the operation.

The Significance of Syphilis in Obstetric Patients.—Fullerton (*Am. Jour. Obst.*, July, 1916) believes that although the Wassermann reaction may be positive, that a patient who has had prolonged and thorough treatment for syphilis may marry after a reasonable time. He believes that the germs of syphilis may be living in the body of the patient without conveying infection. Salvarsan is useful in cutting short the first and second stages of syphilis, but mercury and potassium iodide are necessary for prolonged treatment. In pregnancy drugs given to the mother are conveyed to the fetus in the uterus. After birth the child is best treated by inunctions of mercury, the mother continuing her treatment, and nursing her child. In preventing the ravages of syphilis in parturient women, all women should be thoroughly examined, in each case the placenta should be accurately weighed and examined, and newborn children should be thoroughly inspected. In obstetric clinics the germs of syphilis should be sought for in all suspected cases by microscopic examination. Every effort should be made to follow up cases that show signs of syphilis.

GYNECOLOGY

UNDER THE CHARGE OF

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Role of Douglas's Pouch in the Production of Rectal and Uterine Prolapse and Rectocele.—JONES (*Boston Med. and Surg. Jour.*, 1916, clxxv, 623) believes that Zuckerkandl, Bardenhauer, Moschcovitz and others have demonstrated beyond question an important relationship between the posterior cul-de-sac and its lining fascia and prolapse of the rectum and associated organs. Clinically, Jones recognizes three forms of unusually deep cul-de-sac, the condition which he thinks favors prolapse. The first form is congenital; in it the peritoneum lining the deep pelvis is smooth and closely adherent to the pelvic walls, and the rectum, instead of standing out as a definite organ, is flattened against the sacrum and coccyx. It is with this type of cul-de-sac that prolapse of the rectum occurs in males and in virgins, and prolapse of the uterus and vaginal walls in virgins. The second form is acquired, occurring in multiparæ, as a result of overstretching of the deep pelvic fascia in pregnancy. Here the peritoneum is redundant and not adherent to the pelvic walls, and the rectum stands out distinctly in the pelvis. In the third form there is a small pouch between the rectum and vagina, reaching down to the levators, and usually causing a vaginal protrusion. It is probable, the author thinks, that in the first form the pelvic fascia, which should normally dip down into the cul-de-sac and line it completely, is wanting in this region; in the second form the fascia is present, but is greatly attenuated, while in the third form the fascia is present normally save for a small defect in the posterior portion, through which the intestines force their way to the depths of the pelvis. Jones considers all types of rectal, uterine and vaginal prolapse as hernias, presenting analogous mechanism of formation to hernias in other parts of the body. He reports having seen within the last two years four virgins with the congenital type of deep cul-de-sac. In one there was a prolapse of the rectum, in one a prolapse of the rectum and uterus with a large cystocele, and in the other two a prolapse of the uterus with rectocele. In order permanently to correct the trouble leading to these prolapse conditions, the author considers it necessary not merely to narrow the outlet of the pelvis or to suspend the bowel from above, but to close the hernial sac at what might be termed the internal ring as well. This is accomplished, to some degree at least, by obliterating the cul-de-sac with purse-string sutures of silk, the rectum being also attached to the pelvic peritoneum on either side up to the level of the promontory by silk sutures in the hope of getting support from the many attachments to the peritoneum. In the female the rectum is also sutured to the posterior surface of the vagina and uterus and a ventrofixation is done. The anterior wall of the rectum, being much stretched, must be drawn well up into the pelvis by a guide

suture placed as low as possible in the rectum, and fixed as high as possible. While it might seem that there would be considerable danger of injuring the ureters or great vessels in thus closing the cul-de-sac, Jones says he has never seen trouble from this source in a series of about twenty cases. While the closure of the cul-de-sac in this manner may seem to have little strength, since the sutures include probably nothing but peritoneum, its great value lies in the fact that it throws the weight of the intestines and the intra-abdominal pressure forward onto the symphysis, bladder, and anterior abdominal wall, while an open deep cul-de-sac allows these forces to come against the anterior rectal or posterior vaginal wall.

Etiology and Pathology of Non-tuberculous Renal Infections.—The theory is advanced by CABOT and CRABTREE (*Surg., Gynec. and Obst.*, 1916, xxiii, 495) that practically all renal infections arise as a result of hematogenous invasion of the kidney by the organism in question, these authors considering the ascending or lymphatic routes as practically negligible in importance. They have reached these conclusions following the study of a considerably series of kidneys presenting infections from organisms other than the tubercle bacillus. It has been generally believed in the past that coccus infections of the kidney are usually hematogenous in origin, but it has been rather generally assumed that bacillary infections reach the kidney by ascent from the bladder. This assumption Cabot thinks to be based wholly on its delightful simplicity, but entirely unsupported by scientific evidence. He sees no reason for denying a hematogenous origin for bacillary any more than for coccic infections; in fact, the former has been the more conclusively proven of the two, for the organisms have been repeatedly found in the blood and subsequently in the urine in cases of renal infection, whereas there are but few instances on record where cocci concerned in renal infection have been demonstrated in the blood. He believes also that the common pyelonephritis—mistermed pyelitis—of pregnancy and of children occurs only as a result of organisms reaching the kidney through the blood stream. In contradistinction to the generally accepted views, Cabot holds that the lesions produced by different types of organisms are more or less characteristic, those caused by the pyogenic group (cocci and pyogenic bacilli) differing essentially from those caused by non-suppurative organisms (colon-typhoid group). The former consists of perinephritic abscesses, capsular abscesses, capsulitis, cortical abscesses, septic infarcts, and diffuse suppuration; the latter of acute pyelitis, acute pyelonephritis, chronic pyelonephritis, and pyonephrosis. Infection of a kidney by organisms of both groups will cause a mixture of the lesions, this fact probably explaining the belief that the colon bacillus can produce abscess of the kidney. Cultures containing both colon bacilli and cocci will frequently be interpreted as showing only colon, as this organisms grows with great rapidity and soon obscures the colonies of cocci. The differences in the types of lesions produced by the two groups of organisms are of considerably more than mere academic interest, as Cabot points out, for they have an important bearing on diagnosis. Since the lesions characteristic of the pyogenic group are comparatively shut off from the lower portions of the kidney, and do not involve the pelvic mucous

membrane, pus is rarely found in any considerable amount in the early stages. The lesions of the non-pyogenic group, however, are situated chiefly in the renal pelvis, and result in early appearance of pus with microörganisms in the urine. There is also a marked difference in the effect on phthalein excretion. Infections with the pyogenic organisms involve chiefly the cortex and very little the convoluted tubules, having therefore little effect on the kidney function as measured by phthalein elimination; the chief lesions of the colon group, however, are in the region of the convoluted tubules, and produce sudden and profound changes in renal function. If, therefore, in the presence of clinical evidence suggestive of renal infection, the freshly drawn urine shows cocci in abundance, with a small amount of albumin, a few red blood cells, and many leukocytes or a little pus, with a normal or nearly normal phthalein excretion, the diagnosis of coccus infection is justified. If, on the other hand, examination of the urine shows many bacilli, a little albumin, and much pus, with marked diminution of the phthalein excretion, a diagnosis of colon bacillus infection is unavoidable. Since the suppurative lesions concern those parts of the kidney relatively inaccessible to drugs, their treatment must in the majority of cases be operative, but the lesions of the colon group, involving chiefly portions of the kidney which are relatively accessible to the formalin-containing drugs, a thorough trial of medical treatment in these cases is often advisable. It thus becomes evident that an accurate diagnosis between the two types of non-tuberculous renal infection is of great practical importance from the standpoint of therapy.

Severe Intraperitoneal Hemorrhage from Small Superficial Veins of a Myomatous Uterus.—A most unusual and very interesting case of a condition which very seriously threatened the patient's life has been reported by GERSTENBERG (*Zentralbl. f. Gyn.*, 1916, xl, 795). The patient was a nurse, aged thirty-nine years. While on night duty, taking care of a man whom with great difficulty she was able to lift or move, she was seized one night a few days before her menstrual period with several fainting spells. She attributed these to her run down condition, with the hard work that her night duty entailed. The next night she had another, more severe attack, whereupon she took an alcoholic stimulant and went home to bed, where she was found the next morning in a state of collapse. On examination by Gerstenberg at this time the uterus was found to be small and retroverted, with a hard, roughly spherical tumor somewhat larger than a fetal head, lying above it. The diagnosis was obviously a subserous myoma; the advice given was rest and building up measures, to be followed later by operation. The next morning the author was urgently summoned again, and found the patient pulseless and presenting unmistakable signs of severe internal hemorrhage. By means of active stimulation and abdominal compression it was possible to transport her to the clinic, where the abdomen was immediately opened, practically without anesthesia. The abdominal cavity was found filled with an enormous amount of dark, almost entirely uncoagulated blood, apparently of venous origin. A rapid search of the tubes, ovaries, fibroid tumor, bladder, and intestines failed to show any source of the hemorrhage. Only after throughly cleansing the pelvis and drawing the uterus and

tumor well forward were two tiny slits found in the peritoneum covering the right posterior aspect of the uterus. No blood was coming from them, but they were immediately over small veins, and showed a few attached blood clots. In the absence of any other source of hemorrhage the conclusion was unavoidable that these small veins, engorged from the pressure of the adjacent myoma, and especially so just before the menstrual epoch, had ruptured and had been bleeding more or less continuously since the first fainting attacks three nights before. Only thus could the enormous amount of blood found in the abdomen be explained in view of the very small venous tears. The fact that no hemorrhage was taking place at the time of operation could easily be explained by the exsanguinated condition of the patient. The operation consisted in removal of the fibroid tumor and ligation of the veins. The patient stood it fairly well; the next day the menses appeared, and normal recovery took place. Two and a half months later the patient was in good health save for a certain degree of anemia.

DISEASES OF THE LARYNX AND CONTIGUOUS STRUCTURES

UNDER THE CHARGE OF

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Death of a Child during Suspension Laryngoscopy.—TURNER (*Jour. Laryngol.*, August, 1916) reports this case: A female infant, aged two and a half years, had undergone frequent reintubation for diphtheria during a period of nine weeks. One month after dismission from hospital severe dispnea recurred and she was submitted to examination by suspension laryngoscopy under anesthesia after preliminary injection of $\frac{1}{200}$ grain of atropin. Respiration ceased immediately upon introduction of the tongue spatula. This was removed at once and artificial respiration instituted but without obtaining the desired effect. Tracheotomy was rapidly performed and artificial respiration again resorted to, but without success. The right vocal cord had a somewhat uneven outline, and the mucous membrane beneath it was edematous.

Diffuse Diabetic Ulceration of the Pharynx and Larynx.—ARROWSMITH (*Laryngoscope*, September, 1916) reports a case, the seventh on record it is intimated, in a woman, aged sixty-six years, who, for about a year, had suffered from gradually increasing dysphagia, and at times regurgitated liquids through the nose on attempts at swallowing them. Wassermann tests and sputum examinations negatived syphilis and tuberculosis. Recalling a similar case observed about 1890 in the practice of his friend Dr. Westerbrook, a somewhat similar instance in

his own practice, and a report by Dr. Friedenthal of 5 cases of diabetic ulceration of the pharynx and larynx, he decided that this case belonged in that category. A twenty-four-hour specimen of urine yielded between 4 and 5 per cent. of sugar. The institution of the Allen scheme of treatment produced decided improvement of the glycosuria, but without much change in the local condition. There was ulceration of the uvula, the retina, the posterior wall of the pharynx, and of the laryngeal surface of the epiglottis, and the right arytenoid.

An Epi-hyal Bone in a Human Subject.—GUTHRIE (*Jour. Laryngol.*, July, 1916) reported this case to the Laryngological Section of the Royal Society of Medicine. It occurred in a man about fifty years of age suffering from carcinoma of the upper end of the esophagus. A radiogram by Dr. Oram showed a chain of bones apparently representing a complete "hyoid arch," composed of the basi-hyol (body of hyoid), cerato-hyal (short process of hyoid), epi-hyal, and stylo-hyal, the condition being similar to that seen in the dog.

The Upper Respiratory Passages in Habitual Users of Cocain and Heroin.—RIDPATH (*Laryngoscope*, January, 1916) has carefully examined a number of instances of sniffers of these drugs and finds that the constant use of heroin or cocain upon a mucous membrane produces congestion and tumefaction followed by atrophy and anemia; but the sensibility of the mucous membranes is not affected. Catarrhal affections are less prevalent than in non-users of the drugs. Heroin produces a thin acrid discharge, and cocain causes epistaxis.

Vernal Catarrh Cured with Radium.—DELAVAN (*Radium*, November, 1916), in an article on Radium in the field of Laryngology states that the Radium Institute of London reported excellent results in the treatment of "Vernal Catarrh," patients treated for it with radium having in a large proportion of cases been cured without recurrence, although under observation for a series of years.

Tuberculosis of the Frontal Sinus.—THOMAS (*Jour. Am. Med. Assn.*, July 24, 1915) reports two cases, and states that but five in all have been reported previously and of which he gives a synopsis. Of these five, four terminated fatally, and the other had remained well seven months after operation. Of the author's cases one recovered after two operations and had remained well for more than two years. The other case had been subjected to an extensive intranasal operation two years before consulting Dr. Thomas. It is reported as a case of tuberculous frontal sinusitis, with osteomyelitis, epidural, subdural, and cerebral abscesses resulting in death; a necropsy having been held.

Bleeding Polypus of the Turbinate Body.—MATSUI (*Laryngoscope*, February, 1916), in an article on the "Turbinal Origin of Bleeding Polypus of the Nose," states that he had seen two cases in the clinic of Prof. Ino Kubo, both of which grew out of the lower turbinal and

bled constantly. They are reported in detail and their minute anatomy described and depicted. The tumor parenchyma of these growths is made up of an increase in connective tissue and vessels, and according to the preponderance of one or the other element they may be termed fibroma, angioma or fibro-angioma. They originate from the tissue of the gland stratum of the nose.

Papilloma of the Nose.—Callison (*Laryngoscope*, March, 1916) reports the detailed study of a true papilloma or papillary fibroid springing from the region of the middle turbinate, bulla and infundibulum, in a colored female forty years of age.

Safety-pin Expelled from the Esophagus into the Rhinopharynx During Anesthesia.—Kaufman (*Laryngoscope*, September, 1916) reports the case of a female, aged nineteen years, who swallowed an open safety-pin which was located by roentgen ray at about four and a half inches down the esophagus. Ether was administered and caused much retching and vomiting. Thorough exploration of the esophagus revealed only a few punctate hemorrhages but no pin, It was assumed that the pin had passed into the stomach, but roentgen-ray inspection of the stomach did not reveal the pin. Dr. Bird then roentgen-rayed the head, and detected the pin lodged in the postnasal space, when he removed it with little difficulty.

Treatment of Traumatic Salivary Fistula of the Parotid by Immobilization.—Pietri (*Rev. de laryngol., d'otol. et de rhinol.*, March 15, 1916) describes a number of cases of salivary fistula following gunshot wounds, and details the various treatments instituted. None of them, it is said, can compare with the efficiency of simple absolute repose of the jaws, and feeding the patient with liquids through a tube, the treatment requiring several weeks of patience. Some twenty to thirty cases were observed and cured, and some of the most characteristic of them are pictured in the context.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Dietary Deficiency as the Etiological Factor in Pellagra.—Vedder (*Arch. Int. Med.*, August 1, 1916, xxviii, No. 2) presents the conception of deficiency diseases which has been formed during the study

of beriberi and scurvy. This conception is that there are certain hitherto unknown chemical substances called vitamins which are present in small, varying amounts in foodstuffs. A definite supply of these substances is necessary to maintain normal metabolism, and if a group of people live on a diet deficient in any one of these vitamins the corresponding deficiency disease is produced in a certain number of these people. In the case of beriberi, people living exclusively on over-milled rice, which is deficient in the beriberi preventing vitamins, develop the disease. If a group of people live for a period on food deficient in scurvy vitamins, a number of them will develop scurvy. A deficiency disease is very different from malnutrition, for the scurvy patients' diet may contain an adequate amount of proteins, fats, carbohydrates and inorganic salts and yet may lack certain definite chemical substances, the vitamins, which prevent scurvy. Each individual requires a definite quantity of these vitamins to maintain normal metabolism and this amount varies with the individual. Taking into consideration these facts in respect to known deficiency diseases, scurvy and beriberi, the author puts the query, "Is it possible to consider pellagra as a deficiency disease?" He considers the evidence on this point under the following heads: (1) What analogies exist between pellagra and the two proved deficiency diseases, beriberi and scurvy? (2) Can the evidence pointing toward infection be reasonably explained according to a deficiency hypothesis? (3) Is any deficiency demonstrated in the diet of pellagrins? (4) Can the great increase in pellagra during recent years be explained by the deficiency hypothesis? (1) Pellagra shows great similarity to beriberi and scurvy with regard to clinical and pathological phenomena. The condition of the gums and mouth, the gastro-intestinal lesions, the nervous symptoms in pellagra and scurvy show marked similarity. There are also similarities existing between pellagra and beriberi. The condition of the intestine is somewhat alike in these two diseases, and considerable likeness in the lesions of the nervous system and in the symptomatology referable to the nervous system has been noted. Analogies exist between the epidemiologic data in pellagra and beriberi, both being closely associated with poverty and poor diet. Both these diseases are extraordinarily frequent in institutions, especially hospitals for the insane. The history of the investigations as to the cause of these two diseases is alike in many respects. Although all these analogies prove nothing definite yet they are very suggestive in considering the question of whether pellagra is a deficiency disease. (2) The evidence pointing toward pellagra as an infection may be explained if the hypothesis that pellagra is due to a dietery deficiency be assumed. It may seem impossible that the very pronounced lesions caused by the disease are due to a mere dietery deficiency but the pathologic condition observed in other deficiency diseases, namely, scurvy and beriberi is just as severe. Another piece of evidence pointing to pellagra as an infectious disease is the tendency to self-limitation of the attacks in the absence of specific therapy and presumably without any change in the defective diet that produced the disease. Since it has not been determined which foods contain the necessary vitamins to prevent pellagra it might be possible for the patient to receive some nourishment which has supplied the deficiency and therefore caused improvement. The converse of

this proposition has also been stated that pellagra patients sometimes become worse and die in spite of the fact that they are having apparently an excellent diet. But this diet may have been deficient in the necessary vitamins or the patient may have been unable to assimilate them. Furthermore, it is an authenticated fact that patients with dry beriberi often die although they are fed on the proper diet because the disease has progressed to such a point that death is imminent. The fact that pellagra appears in the spring and improves during the summer and fall to recur again the next spring points distinctly toward the dietary hypothesis and not toward the infection theory as no known infection acts in this way while beriberi acts exactly in this way. This action of the disease is thought to be due to the dietary habits of the people, that is, the poor live chiefly on flour, cornmeal, canned goods and salt meat in the winter and such diet after several months produces the lesions which appear in the spring. When fresh vegetables and fruits appear in the late spring and early summer, the deficiency is remedied and the condition improved. Although the statement that in about 90 per cent. of the cases studied there was personal contact or association with a previous case of pellagra seems to be strongly in favor of the infectious nature of the disease, it is really of little significance, for 43.5 per cent. of these contact cases have occurred among members of the same family who have presumably the same diet. As to the remaining 46.5 per cent., where contact with a case outside the family has been demonstrated, it may be said that pellagra is so common in many parts of the south that really every one has come into contact or associated with a case of pellagra. The fact that a very large part of the population has been in contact with cases without developing the disease takes away from the importance of contact as an etiologic factor as does the fact that doctors, nurses and attendants in closest contact seldom acquire the disease. Density of population seems to bear no relation to the spread of pellagra, as in Spartanburg, S. C., the mill villages present a rate of 142 cases per 10,000, while the rest of the city population living under the same conditions of congestion gives only 29 cases per 10,000 inhabitants. The greater number of cases in the mill villages is explainable if it is granted that pellagra is a deficiency disease, as the population of these villages is a homogeneous group of people of the same economic status living on a poor class of food. The Pellagra Commission collected considerable evidence to show that proximity of domicile was an important factor in the incidence of pellagra and that, since this was true, the disease must be of infectious origin. They found that new cases of the disease developed almost exclusively in small foci within which one or more cases of the disease already existed, the greatest number occurring in the first zone, the next in the second and the least in the third. However, it seems that this incidence of cases can be explained if the disease is caused by a dietary deficiency as the majority of people living in the house with a pellagra patient, that is, those included in Zone 1, would be exposed to the same deficiency of diet. The large number of the cases in Zone 2 is explained by the fact that pellagra is commoner among the poor than among the well-to-do and the poor people live in the same part of a town or village and so are practically segregated. Therefore there would naturally be more cases in the neighborhood immediately

surrounding the house where a case existed than there would be in a remote and more prosperous section of the city. While there is a tendency for pellagra to occur in that part of a community having primitive systems of disposal rather than in the part having proper sewage systems, this proves nothing, for the poorer sections which have the less developed systems, are the sections where poverty and, consequently, a poorer dietary exist. The commission has shown a tendency to believe that, because they have not found any special food to be the causation factor, the disease could not be of dietary origin, and that if it were a deficiency disease, fresh meat, milk and eggs might be supposed to supply this deficiency. They have collected evidence to show that of the 82 persons in families using fresh meat daily, 4.88 per cent were pellagrins. This evidence is not considered conclusive because (1) it does not consider in sufficient detail the quantities of the various foods used; (2) it considers individual foodstuffs and their influence rather than the total diet; (3) the possibility that wheat-flour is mainly responsible for the deficiency has not been investigated sufficiently; (4) in an investigation of the diet of pellagrins it was found that among both the poorer and the well-to-do cases, there were some circumstances as a result of which the patient had lived on a very one-sided diet, in every case consisting chiefly of flour, corn products, or potatoes, with the addition of salt meat or canned vegetables; (5) pellagra is becoming more common in the south every year and an attempt has been made to explain this in accordance with the hypothesis that it is due to a dietary deficiency. The following facts indicate that changes have occurred in the dietary of the population as a whole during the last ten years: (1) The population itself has increased greatly, especially the industrial population among which the dietary is distinctly inferior to that of the remainder of the population. (2) There has been a great change in the purchasing power of the population, but there has also been a greater increase in the price of food so that there is a distinct tendency for poorer people to cut down the consumption of fresh meat, eggs, vegetables, and fruit and to increase the consumption of such staples as cornmeal, hominy, and flour. (3) Such tendencies were actually demonstrated in a number of cases investigated and statistics were collected which showed that the per capita consumption of fresh meat and of pure lard had decreased very considerably in the last ten years while the consumption of canned goods, cornmeal, and flour had increased. As a result of the investigations the conclusion is reached that the hypothesis that pellagra is caused by a dietary deficiency seems very plausible, and must be considered in subsequent studies of the disease.

How Tuberculosis is Contracted.—Smith (*Jour. Med. Research*, 1915, xxxii, 417) states that the beginning of the tuberculous changes in the wall of the minute bronchi is not in itself proof that the bacilli are air-borne, nor does it prove that inhaled bacilli have penetrated directly the mucosa of the minute bronchia. The development of tuberculosis in the apical lobes in man is best accounted for by the less active aëration and less active lymph current. Rib pressure may contribute toward fixing the bacilli. Bacilli, deposited either from the

air or the blood in other lobes are either destroyed or promptly carried by the lymph current to the lymph nodes, where they are gradually destroyed. The phenomenon of phthisis in man is strong evidence that the human being possesses a relatively high degree of resistance to the tubercle bacillus.

Arsenic in "Chemically Pure" Zinc.—Myers (*Public Health Reports*, October 6, 1916, vol. xxxi, No. 40) examined eight samples of metallic zinc purporting to be chemically pure and free from arsenic and found them to contain arsenic. After specifications were submitted requiring arsenic-free zinc, samples of impure zinc were also received. Amounts varying from 1 to 10 parts per 1,000,000 of metallic arsenic were found. This fact shows that it is necessary for analysts in food, drug, and public health laboratories to examine all chemicals for themselves.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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The Specificity of Streptococci.—Much has appeared in recent literature indicating the importance of streptococci in human disease. Various authors have approached the subject from different angles. Some have been content with isolating these microörganisms from tissues and offering this evidence as demonstrating the causative factor in the disease, others have studied the streptococci from various sources hoping to find a means of classification which would indicate their biological and pathogenic qualities, a third group has attempted to distinguish the streptococci only by their ability to locate in particular regions and induce disease in them. Henrici (*Jour. Infect. Dis.*, 1916, xix, 572) studied 53 strains of streptococci from various sources, comparing the cultural characters with the pathogenic qualities as exhibited in infection of rabbits. The streptococci used were classified according to the method of Andrewes and Horder using the hemolytic test to divide the two main groups. Two hundred and twenty-five rabbits were inoculated with varying amounts of culture and were autopsied at intervals of two to ten days. Careful observations were recorded and tissues were studied microscopically. The author found lesions in the brain, heart, arteries, muscles, joints, and kidneys. In no

instance were the lesions in any one of these tissues produced by a single type of streptococci alone. It was quite remarkable that inflammatory processes induced by the streptococcus pyogenes were not uncommonly identical with those produced by the viridans group. In only a few instances were abscesses found. From these results it would appear that the strains of hemolytic streptococci used in the experiments were of low virulence. The author could find no evidence that any of the organisms tested showed an elective affinity for particular tissues. Valvular heart lesions developed in about 9 per cent. of the rabbits inoculated with non-hemolytic strains and in 11 per cent. of those receiving hemolytic streptococci. Myocardial lesions simulating those found in acute rheumatic fever occurred with equal frequency in animals receiving the hemolytic or the non-hemolytic varieties. He concluded that from the evidence obtained from the experiments we are not justified in recognizing any particular class of streptococci as specific for rheumatic fever. In general he found the hemolytic streptococci more virulent than the non-hemolytic, although the two classes localize in the same tissues with equal frequency.

Multiple Telangiectatic Hemangiomata.—Cutaneous hemangiomata are quite common and are quite frequently seen about the face. Many of them appear to have a congenital origin although they may not be observed until, by increase in size, they form a definite tumor mass in early years of life. It is not uncommon to find these vascular tumors progressively enlarging and sometimes even recurring after removal. The question of malignancy has given rise to much discussion although metastatic growths have not been demonstrated. This type of tumor is not common in the internal organs. SCHMITT (*Cent. f. Path.*, 1916, xxvii, 145) describes a case of hemangioma arising in a child of three months and making its simultaneous appearance in two situations. The one was lying in the orbital fossa and was recognized clinically and removed by operation. At autopsy, a few days later a second mass was found along the trachea in close proximity to the right thyroid. The histological character of the tumor simulated an angioma simplex with evidence of progressive extension of the capillary structure into the surrounding tissues. This infiltrating character of the growth has led numerous authors to classify these tumors among the sarcomata. The capillary structures forming the main element in the tumor are seen as wormy masses with thick walls composed of endothelial overgrowth. At times the lumina are well preserved or even dilated, and at others, the lumen is occluded by the proliferated tissue so that no blood elements are to be found within them. A number of other cases of multiple angiomata have been described by other authors. In some of them skin tumors were associated with similar structures in the internal organs. The wide distribution of the tumors in some of these cases is quite remarkable, but yet there is no evidence of true metastatic implantation. It would rather appear that we are dealing with multiple primaries.

Histological Lesions in Pellagra, Fasting and Experimental Scurvy.—Not a few of the studies carried out upon nutritional diseases and particularly pellagra have been made by the Italians. In fact, much

of the earlier work indicating the relation of corn to pellagra began with the studies of Ballardini. For the group of manifestations arising from the eating of deteriorated corn they have coined the term "maidism." According to its use the word may be applied to various clinical and pathological manifestations making their appearance at various stages during the nutritional disturbances. RONDONI and MONTAGNANI (*Sperimentale,* 1915, lxix, 659) have again reviewed the pathological changes occurring not only in "maidism" but also in scurvy and fasting. They point out that a comparison of the histological lesions is essential for a proper understanding of each. The fasting experiments were made upon guinea-pigs, observations being made upon both the acute and chronic types. The outstanding features were general emaciation, atrophy of organs, especially spleen and liver; enlargement of adrenals. In another series of experiments, guinea-pigs were fed on corn flour and histological studies were made upon the animals dying spontaneously. In these animals petechial hemorrhages were occasionally seen in various organs. The liver showed evidence of degeneration as well as proliferation of the bile ducts and liver cells. Central hyperemia was also common. The heart, lungs, intestine, kidney and pancreas showed no evidence of change other than occasional hemorrhages. The spleen showed evidence of fibrosis about the central arteries and the organ was slightly increased in weight though not in size. The authors claim to have observed fairly constant changes in the thyroid, consisting of a hyperemia, hyperplasia and increase in the colloid content. Occasionally patches of fibrosis also appeared within the thyroid. A similar hyperemia and hyperplasia was found in the adrenals, being particularly marked in the cortex. The medulla showed but little change. The important changes observed in the central nervous system were in the cord in which the ganglion cells of the anterior horn showed evidence of degeneration. Less marked degeneration was present in the cerebellum. They conclude that exclusive corn feeding may produce lesions more or less serious in many organs and tissues, which explains the cachexia and death of the animals. Of particular interest were the lesions of the thyroid and suprarenal in which a degree of sclerosis may be associated with the functional disturbances. The sclerosis of the thyroid differentiates the "maidism" from simple emaciation. "Maidism" can be differentiated from scurvy by the presence of the sclerosis in the former and the predominant hemorrhages in the latter. Furthermore the degenerations in the nervous system are more marked in "maidism." The authors suggest that "maidism" may be the result of toxic substances present in good corn or the deficiency in corn of a certain unknown product necessary for the normal development and function of the glands of internal secretion.

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ORIGINAL ARTICLES

EPIDEMIC POLIOMYELITIS: ITS NATURE AND MODE OF INFECTION.[1]

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NEW YORK.

The present time, while we are under the influence of the serious epidemic of the past summer and autumn, may be the most favorable time to impress certain essential facts regarding poliomyelitis upon the general medical profession.

Epidemic poliomyelitis, or infantile paralysis as the disease is variously and on the whole erroneously called, is becoming increasingly familiar to us. Indeed, each year since 1906 the disease has prevailed in some part of this country in severe or even epidemic form. It is, of course, true that epidemics had occurred in this country before, but their relatively small size and their infrequency marked them off sharply from the epidemics prevailing since 1906. The recent experience America has been passing through is, however, not exceptional, since during the same period the disease has become more prevalent throughout the world—affecting the European countries, the West Indies, South America, the far East, Australia, etc. This very wide and general distribution of the disease can be attributed to the endemic focus in northern Europe, ever becoming more and more active, which culminated in the severe epidemic

[1] Part of the discussion on Poliomyelitis held at the College of Physicians of Philadelphia, December 6, 1916.

outbreak in Sweden of 1905. It was the epidemic of 1905 which was the immediate forerunner of the pandemical occurrences mentioned.

Unfortunately, very considerable uncertainty exists still regarding the character and nature of this epidemic disease. Because of its recent introduction into this country a large part of the medical profession has lacked familiarity with it. On the surface it is not so easy to identify the severe forms of the epidemic disease with the occasional and sporadic instance of infantile paralysis arising in every considerable community, and yet essentially they are one and the same disease—that is, they are due to a common etiological agent, in the same manner as the sporadic instances and epidemics of cerebrospinal meningitis are both caused by the meningococcus.

Considerable difficulty and confusion have been introduced into the subject by the common names for the epidemic disease. As is usual, names express conceptions, and in this case the names chance to be misapplied. So long as the disease is conceived of as one attended by paralysis, which in turn is due to lesions of the gray matter of the spinal cord (or brain), a large number of cases are excluded altogether. Because we have now learned, thanks especially to Wickman, who studied the Swedish epidemic of 1905, that many cases of the disease, perhaps the majority, in epidemic times are not associated with any paralysis whatever. I shall not elaborate this point; I introduce it merely to emphasize its importance in respect to the public health control of the disease. Others who follow will doubtless refer to this same point. But I wish to leave you under no doubt that the disease we are considering appears in a variety of clinical forms, some of which are very slight and trifling and others of the profoundest severity.

If I should be called on to define epidemic poliomyelitis—so-called—I should call it an acute infectious and communicable disease, attended sometimes, but by no means always, with involvement of the central nervous organs, as a result of which incident paralysis often results. The parts of the central nervous organs most frequently involved are the meninges, with which may be and often is associated injury to the gray matter of the spinal cord and brain leading to muscular paralysis.

In its essential nature the disease is an infection. We now know, thanks especially to the employment of monkeys for inoculation, that the microörganism causing it is very minute, filterable, indeed, but probably not invisible. That is, by particular cultivation methods a minute anaërobic microörganism has been secured which fulfils Koch's law of causation. But I feel that it is better to wait until this experimental work has been confirmed in other countries in which epidemic poliomyelitis occurs before proclaiming the microorganism as the established cause of the disease.

But what is of first importance is the discovery of the manner in which the microbic cause of poliomyelitis enters and leaves the body,

because the mode of infection so largely controls the methods of prevention to be taken.

Tests carried out on monkeys have proved beyond doubt that the virus of poliomyelitis, so-called, exists regularly upon the mucous surfaces of the nose and throat and often of the intestine, with the discharges of which it may gain access to external nature. It has also been traced on the upper respiratory mucous membrane of healthy persons who may act as carriers, and has been found in several instances in the tonsils removed by operation several months after recovery from the acute disease, so that the existence of so-called chronic carriers has also been indicated.

In spite of doubts and disputes concerning the mode of infection, this much we know positively, and hence should take sanitary measures accordingly: the infectious agent can and does enter and leave the body by the upper respiratory mucous membrane, and may at least leave the body with the intestinal discharges. Whether there are still other avenues of infection we do not know. Neither do we yet understand the tendency of the disease to reach its height in the late summer and early autumn months. But in attempting to interpret that phenomenon we must still keep in mind that increasing intensive study is showing more and more that cases of the disease extend throughout the winter, and in two instances at least midwinter epidemics occurred in Sweden and Norway.

Under the circumstances the disease is to be regarded as communicable from person to person—by the infected sick in any of the many forms in which it appears and by healthy persons who may be contaminated by the sick. It is, of course, not possible to control by isolation all exposed persons. But a large part of the problem of the public control of the disease rests on early and accurate diagnosis, and the reduction of exposure of persons who may become potential healthy carriers of the agent of infection.

What is greatly to be desired is a simple, readily applied biological test which would give practically unmistakable answer as to whether poliomyelities was present or not. Such a test has not yet been devised. We cannot use the cultures for this purpose because they are too difficult to obtain; we can, however, use lumbar puncture, which in 90 per cent. or more of instances yields a definite result. In general, it may be stated that, irrespective of the severity of the symptoms, lumbar puncture yields in cases of poliomyelitis a fluid, usually clear, but showing either morphological or chemical changes, or both these changes simultaneously. The mononuclear cells tend to be increased and globulin often is present. These changes in the cerebrospinal fluid, especially during periods of epidemic, should be regarded as presumptive evidences of poliomyelitic infection and measures of public protection taken accordingly. Moreover, as beginnings are being made in respect to a specific form of treatment, the employment of lumbar puncture and study of the

changes in the cerebrospinal fluid are affording the basis for the application of treatment at the more favorable periods, before contingent paralysis has appeared, which may often determine whether the treatment will be effective or not.

I must ask your indulgence for presenting a paper merely in outline. If the points presented impress you at times as being perhaps aphoristic, may I remind you that there exists competent, as I believe, clinical and experimental data for them all.

SOME PRACTICAL CONSIDERATIONS IN THE ADMINISTRATIVE CONTROL OF EPIDEMIC POLIOMYELITIS.[1]

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There are obvious practical limitations to the application of scientific laboratory and clinical knowledge in the public control of communicable disease. Furthermore, when the means of transmission, of immunization, and of detection of carriers of a disease are lacking the resources of the public health officer are sadly restricted. In view of the keen public and professional interest in the recent severe epidemic of poliomyelitis and the advantages which should accrue from a frank admission of the accepted facts, I venture to present the following statement of the situation as it must face professional advisers of public policies, so far as this particular disease is concerned.

The use of popular educational publicity will go far to teach parents the necessity of obtaining competent medical advice immediately upon the appearance of fever, pain, digestive disturbance, or acute symptoms of any kind in little children. Such advice is applicable at all times, but is listened to with respect only when the public is interested or is aroused to a particular danger. The benefit of following such advice is seen at once in the earlier home recognition of the common infections of childhood, a quicker appeal to the family physician, and in the more prompt and general reporting of communicable diseases of children to the health authorities. To the adoption of such advice we may attribute the decided reduction of the infectious diseases (pertussis, measles, diphtheria, scarlet fever, and infantile diarrhea) during the past summer.

The health officer can, with propriety, warn parents against allowing the indiscriminate association of children, and particularly against contact with children in whose families there are acute

[1] Read before the College of Physicians of Philadelphia, December 6, 1916.

illnesses of any kind. As a type of simple, direct, practical advice the following extract from a circular of information to the public will serve for issue through the field force and the newspapers:

INFORMATION FOR THE PUBLIC.*

"Infantile paralysis (poliomyelitis) is a catching disease. How it is spread is not yet definitely known. In most cases the disease is probably taken directly from a sick person, but it may be spread indirectly through a third person who has been taking care of the patient or through children who have been living in the same household.

The early symptoms are usually fever, weakness, fretfulness or irritability, and vomiting. There may or may not be acute pain at this time. Later there is pain in the neck, back, arms, or legs, with great weakness. If paralysis is to occur it usually appears from the second to the fifth day after the sickness begins. Many cases do not go on to paralysis.

The germ of the disease is present in discharges from the nose, throat, and bowels of those ill with infantile paralysis even in the cases that do not go on to paralysis. It may also be present in the nose and throat of healthy children from the same family. Do not let your children play with children who have just been sick or who have or recently have had colds, summer complaint, etc. For this reason children from a family in which there is a case of infantile paralysis are forbidden to leave their home. If you hear of their doing so report it at once to the Department of Health.

Persons over sixteen years of age, from families where there are cases of poliomyelitis, may continue at work unless their business has to do with the preparation or handling of food or drink for sale.

If you hear of a case in your neighborhood and the house is not placarded, notify the Department of Health.

How to Guard Against the Disease. In order to prevent the occurrence of this disease, parents should observe the following rules:

Keep your house or apartment absolutely clean.

Go over all woodwork daily with a damp cloth.

Sweep floors only after they have been sprinkled with sawdust, old tea leaves, or bits of newspaper which have been thoroughly dampened. Never allow dry sweeping.

Screen your windows against flies, and kill all flies in the house.

Do not allow garbage to accumulate, and keep pail closely covered.

Do not allow refuse of any kind to remain in your rooms.

Kill all forms of vermin, such as bed-bugs, roaches, and body lice.

Pay special attention to bodily cleanliness. Give the children a bath every day and see that all clothing which comes into contact with the skin is clean.

* Extract from leaflet issued by the New York City Department of Health, July, 1916.

Keep your children by themselves as much as possible. Do not allow them to visit moving picture shows or other places where children may gather.

Children should not be kept in the house; they should be out-of-doors as much as possible, but not in active contact with other children of the neighborhood. Do not take them on a street car, unless absolutely necessary, or shopping.

Do not allow your children to be kissed.

It is perfectly safe to let your children go to the parks and playgrounds if only two or three of them play together; they should not play in large groups, and you should not let them come into contact with children from other parts of the city.

Remember that children need fresh air in the summertime, and outdoor life is one of the best ways to avoid disease.

If there is a public shower bath in a school in your vicinity, send the older children there every day for a shower bath. This is perfectly safe and will help keep them in good health.

Give your children plain, wholesome food, including plenty of milk and vegetables.

Keep the milk clean, covered, and cold. Do not allow the milk or any other food to be exposed where flies may alight upon it.

Wash well all food that is to be eaten raw.

In Case of Sickness. Remember that during the hot weather children are apt to have stomach and bowel troubles. If your child is taken sick with loose movements of the bowels, or with vomiting, do not at once fear that it must be infantile paralysis; it may be simply digestive disturbance. Give the child a tablespoonful of castor oil and plenty of cool water to drink, and *send for the doctor at once.*

If you cannot afford a doctor's services, telephone the Department of Health and one will be sent free of charge.

If a doctor or nurse from the Department of Health visits your home, give them all the information you can. They are sent to show you how to keep your children well.

Do not give your children patent medicines or buy charms of any kind to ward off the disease. *The best preventive is cleanliness and strict observance of the rules that have been given.*"

And when the advice has been given, the most unexpected and extravagant applications of it may ensue. Many a family of children was housed for weeks, often in tight-shut rooms, even in July and August, the children's pale faces pressed against the window panes, mute evidence of their unreasonable imprisonment.

The mother whose neighbor's children across the tenement hallway are attacked with poliomyelitis, one of the four dying of the disease and another a permanent cripple, is not easily per-

suaded that the warning of the health officer in papers, circulars, and by the visit of the nurse does not logically demand home isolation of the well during the epidemic. When the visiting nurse is met by a door slammed in her face, where previously welcomed as the family's guardian and friend, we see how the laity reacts to the warning against contacts, the nurse being supposed to be constantly carrying disease from family to family. In the main, however, such educational propaganda is valuable but beyond this there is to my knowledge no warning or advice which can fairly be considered to produce any tangible results before or during an epidemic of poliomyelitis. There are sound reasons for advising the screening of living and eating premises against insects. There is always advantage in maintaining the person, the home, and the public highway in cleanly condition. Cooked food is safer than raw food for children in summer.

Up to the present moment there is no practical experience which can be claimed to show that environment, *i. e.*, housing, street dust, sewage, garbage, water, food supply, domestic or wild animals or insects, whether blood-sucking or not, has any relation to the origin or dissemination of poliomyelitis.

Aside, then, from the teaching of the principles of personal hygiene and avoidance of fatigue, the need of obtaining medical services in the presence of sickness and the probable advantage of avoiding contact between children during an epidemic, the hands of the health officer are tied by his ignorance of the means of transmission and the identity of carriers who do not show evidence of sickness.

When a case of sickness occurs the difficulties do not diminish. Diagnosis cannot be said to be either easily or positively made unless there is a paralysis present at some time. The increasing probability that there are as many non-paralytic as paralytic cases does not satisfy the parents of children, who naturally look for some positive proof, specific for the disease when it is diagnosed in a non-paralytic form, before willingly relinquishing their child to hospitalization or submitting to a quarantine.

We have no specific diagnostic test, though the spinal fluid considered in connection with a good history and definite clinical symptoms will, during an epidemic, even in the absence of paralysis, justify a positive diagnosis.

The discordant opinions of other physicians, whose services are commonly obtained by a resentful family when report of a case of poliomyelitis is made by the regular physician in attendance, bring the official diagnosticians of the Health Department into difficult relations with their fellow-practitioners, and not uncommonly result in feelings of resentment on the part of the family, which in one instance led to the institution of habeas corpus proceedings.

In a disease so little seen or recognized in the past in general practice it is not uncommon to lose that agreement and approval

among physicians without which it is obviously impossible to obtain public compliance with restrictions or professional coöperation with health officers so necessary for early and universal notification.

In the early days of an epidemic inevitably the diagnosticians of the Department of Health see more cases in a very short time than do other physicians, and if thoroughly trained under capable supervision they rapidly become experts to a degree which temporarily at least makes them appear critical of their fellow practitioners.

This difficulty is readily met by organizing public medical clinics and lectures at various points throughout the city where pediatrists, neurologists, and Health Department diagnosticians may give personal instruction in the early and differential diagnosis of poliomyelitis.

The prompt issue of leaflets of information to physicians, early in the epidemic, will enlist their coöperation and give the essential facts in a form for ready reference. Such a circular as the following proved a helpful starting-point with many for a more thorough understanding of the disease with which, at least in its epidemic manifestations, few were at all familiar.

INFORMATION FOR PHYSICIANS.*

"*Early Diagnosis.* The attention of physicians is called to the necessity of an early diagnosis of all cases of poliomyelitis. Early recognition and strict quarantine are the chief weapons against the disease.

Reporting of Cases. All suspicious cases must be at once reported to the Department of Health by telephone, to be followed within twenty-four hours by a written report. The ability of the Department of Health to limit the spread of the infection depends upon the immediate reporting of every suspicious case.

Age of Persons Affected. It should be remembered that this disease may occur at all ages, although the great majority of the cases are found in children between the ages of one and five years.

Type of Disease. Peabody, Draper, and Dochez, of the Rockefeller Institute, give the following classification of the disease:

1. The non-paralytic or so-called abortive cases.
2. The cerebral group, with spastic paralysis.
3. The bulbospinal group.

Methods of Infection. The experiments of Landsteiner and Popper in Germany; Kling, Pettersson and Wernstedt in Sweden, and of Flexner and Noguchi in this country have proved that the disease is transmitted by the secretions of the nose and mouth and the bowel discharges of an infected person. The infection is transmitted through the mouth, tonsils, and nasal mucous membrane.

Contacts and Carriers. It must be remembered that while the transmission of the *disease* from a patient to other members of the same family is not usual, transmission of the *virus* is common.

* Extract from a leaflet issued by the New York City Department of Health, July, 1916.

Experience warrants the assumption that in addition to direct contact the disease is spread by carriers, usually children, who are themselves immune but who harbor the infective material in their nasal or mouth secretions.

Symptoms. Early symptoms to be regarded as suspicious are: Fever, vomiting, slight diarrhea, listlessness, unusual fretfulness, and drowsiness. Later and more characteristic symptoms are: The appearance of weakness in any extremity, skin and muscular sensitiveness, spinal pain, especially on flexion, apparent or real rigidity of the neck muscles, Kernig's and MacEwen's signs.

Course and Duration of Disease. Paralysis appears usually before the sixth day of the illness; it may occur as early as the first day. Other symptoms, except spinal and muscular pain and rigidity and skin sensitiveness, rarely persist.

Non-paralytic or So-called Abortive Cases. Non-paralytic or so-called abortive cases are very frequent. In some epidemics they constitute from 25 to 50 per cent. of the diagnosed cases. The children have the early symptoms just mentioned, perhaps also the muscular tenderness and spinal pain. If carefully observed it may be noticed that they develop a paralysis of one or more groups of muscles, but that instead of the paralysis continuing it all disappears within a few hours. It is obvious that the recognition of such cases is of extreme importance in controlling the spread of the disease. The diagnosis of such cases is greatly facilitated by an examination of cerebrospinal fluid obtained through lumbar puncture.

General Care of Patient. Complete rest is of the utmost importance for either paralyzed or weak muscles for the first five or six weeks. Every effort must be taken to make this rest complete. The limb must not be allowed to drag on a paralyzed muscle. It should be supported by pillows or pads or bandages. There seems to be a greater tendency to atrophy if casts are used. A dropped foot may be supported by a sandbag or pillow; small rolls placed under the knee often hold the leg in a more comfortable position. The weight of the clothing should be kept off the legs by hoops or other device. If the head is somewhat retracted and the patient desires to lie on his back, he may sometimes be made more comfortable by a small pillow placed under the shoulders, allowing the head to fall back. The value of electricity for treatment in the first six weeks is very doubtful. In many instances it may do harm. Massage or passive movements should not be begun for at least five or six weeks and then should be used with great care. In cases that show a tendency to clear up rapidly the child should be kept in bed for some time after the ability to use the muscles returns. It should never be encouraged to try to stand or to use the muscles otherwise until a considerable time has passed.

Period of Incubation and Duration of Disease. The incubation period has been officially set at two weeks. Non-immune, infected persons usually manifest symptoms of the disease in from five to ten

days after exposure. The average period of incubation is seven days. The early symptoms, noted above, usually last from one to seven days. Quarantine of the patient will be maintained for a period of at least eight weeks.

Prevention of Spread of Infection. 1. The children from an infected family will be confined to the house. (See "Quarantine.")

2. During the continuance of an epidemic of poliomyelitis children should not be allowed to congregate in public places.

3. Fresh-air outings or vacation camps are allowed, if kept under competent medical supervision, with an adequate physical examination of each child before enrolment and the exclusion of any child from an infected family.

4. Absolute cleanliness of all homes is essential; such cleanliness should include:

(*a*) Screens in all windows.

(*b*) Flies kept out of all rooms.

(*c*) Thorough cleanliness of all floors, woodwork, bedding, and clothing.

(*d*) Avoidance of dust (all sweeping should be done after the floors have been sprinkled with sawdust, bits of newspaper, or tea leaves, all thoroughly moistened).

(*e*) Garbage cans kept closely covered and washed out in hot soapsuds after they have been emptied.

(*f*) No refuse, either of food or other waste, allowed to accumulate.

5. Personal habits of cleanliness are essential; the hands should be washed before each meal, after each visit to the toilet, and before going to bed. Children should be warned about putting the fingers into the mouth or nostrils.

6. When sneezing or coughing, a handkerchief should be held over the mouth. Kissing of children is also a dangerous practice and should be avoided.

Procedure to be Followed in Each Case. 1. Isolation of patient: Complete isolation of the patient must be maintained until terminated by order of the Department of Health.

2. A separate room must be provided for the patient. No one must be allowed in this room except the attending physician, the nurse, and the representative of the Department of Health.

3. Care of patient's room and surroundings: (*a*) All rugs, carpets, draperies, and unnecessary furniture must be removed before the patient is placed in the room.

(*b*) All windows must be screened.

(*c*) The sick room must be kept well aired at all times.

(*d*) The woodwork must be wiped daily with damp cloths. Under no circumstances must the floor be swept when it is dry. It should be sprinkled with sawdust, bits of newspaper or tea leaves, all thoroughly moistened and then carefully swept so that no dust may arise.

(*e*) Toys and books used by the patient must be destroyed by burning after recovery or death.

(*f*) Household pets must not be allowed in the room.

4. Care of bedding: All cloths, bed-linen, and personal clothing which have come into contact in any way with the patient must immediately be immersed in a 5 per cent. solution of carbolic acid and allowed to soak for three hours. They may then be removed from the room and must be boiled in water or soapsuds for fifteen minutes.

5. Care of discharges from body: A sufficient supply of gauze or clean linen or cotton cloth must be provided and all discharges from the nose and mouth of the patient received on these cloths. After use they must be immediately burned or boiled. Bowel discharges and urine must be covered at once with chloride of lime and then disposed of by emptying into a water closet.

6. Care of utensils used by patient: Plates, cups, glasses, knives, forks, spoons and other utensils used by the patient must be kept for exclusive use and under no circumstances removed from the room or mixed with similar utensils used by others. They must be washed in the room in hot soapsuds and then rinsed in boiling water. After use the soapsuds and water must be thrown into the water-closet.

7. Nurse: A trained nurse or competent attendant must be in sole attendance upon the patient. She must not be allowed to mingle with the rest of the family but must be isolated with the patient. The hands of the nurse must be carefully washed in hot soapsuds after each contact with the patient and before eating.

8. Termination of case: After the case has been ordered terminated by the Department of Health the following procedure must be followed:

(*a*) The entire body of the patient must be bathed and the hair washed with hot soapsuds. The patient should then be dressed in clean clothes (which have not been in the sick room during the illness) and removed from the room.

(*b*) The nurse should also take a bath, wash her hair, and put on clean clothes before mingling with the family or other people.

Action Taken by the Department of Health in Each Case. Placarding: Every house will be placarded without exception. In private houses one placard is placed on the street front (outside of house), and one placard is placed on the door entering the room patient is in. In tenements three placards are affixed, one on street door, one in entrance hall, and one on door of apartment. All placards are dated.

Quarantine: In all families where a case of poliomyelitis has occurred all other children under sixteen years except those who have had the disease are to be quarantined in the home until two weeks after the termination of the case by death, removal, or recovery.

The patient, whether at home or in hospital, must be quarantined for eight weeks from onset of disease.

Children under sixteen years of age who have been, but no longer are, exposed to infection will be quarantined for fourteen days.

Removal to hospital: No case is to be left at home unless the following conditions are complied with:

(*a*) There must be a private physician in attendance regularly.

(*b*) Persons attending patient must obey quarantine rules; must not do any housework, marketing, or leave premises.

(*c*) Patient and attendant must have separate rooms.

(*d*) All windows of rooms used by patient must be screened.

(*e*) The family must have a separate toilet for its exclusive use.

(*f*) Quarantine regulations must be strictly observed by patient and other children.

Deaths: In case of death prompt burial is required, the coffin must be sealed as in deaths from other contagious diseases, and the funeral must be strictly private. Church funerals are prohibited.

Spinal puncture: Physicians desiring the services of a consultant to perform lumbar puncture and report on the examination of spinal fluid should telephone to the Department of Health."

Once the diagnosis is accepted by family and physician, the next step is fairly clear. Contact is effectively prevented in hospitals and less consistently in the home even when there is unusually intelligent and favorable care. Removal of the sick child to a hospital, if accepted by parents, is a simple matter; if opposed, it may prove the irritant which sets a whole community against the simplest and gentlest measures of restraint. Anything which causes antagonism of the public to the policy of reporting and removal to isolation hospitals, develops deception, hiding of cases, and such methods of obstruction as to frustrate to a great degree any approach to successful separation of the sick from the well. Once the case is under surveillance at home or in hospital the uncertainty as to a reasonable period of isolation becomes prominent. The parents and the press ask embarrassing questions. What is the duration of infectiousness? If six weeks is not certain is six months any more so? Why eight weeks in New York City and six weeks elsewhere throughout the country? Six weeks has been generally agreed to as a suitable isolation period dating from the day of onset, the only adequate basis for this being that, after six weeks, infectious material has rarely been obtained from artificially infected monkeys. We established the isolation period at eight weeks in New York City at the beginning of the epidemic, to impress the public with the seriousness of the danger and partly to obtain a greater percentage of voluntary hospital admissions. There is no reason to believe that eight weeks' isolation of infected

individuals is of any more value than the more commonly accepted six weeks' period.

How long the incubation period? Is a child recovered from paralysis still infectious? How long before the disease expresses itself has a patient been infectious? Only provisional answers can be offered to any of these questions.

Whether or not hospitalization justifies itself as a sanitary measure to protect susceptibles against exposure to infected individuals, it has resulted in definite and marked improvement over the usual treatment given to the children of the poor in their homes during the acute stage of the disease and in the prevention of much avoidable subsequent deformity.

There are too many undetermined factors which may have played a part, to draw positive conclusions as to the effect of hospitalization upon the distribution of poliomyelitis in New York, but it is certainly suggestive that in the Borough of Manhattan where more than 90 per cent. of all reported cases were removed to hospitals, the case incidence of the disease was 0.94 per 1000, while in Brooklyn, where not over 50 per cent. of the cases were taken from their homes for isolation purposes, the case incidence was 2.24 per 1000 of the population.

The unusual opportunity offered by the assembling of such a number of acute cases and holding them for a long isolation period should not be lost to the medical profession. Postgraduate clinical teaching should be carried on as systematically as the emergency conditions prevailing will permit.

More than 800 physicians visited the wards of the Willard Parker Hospital, where, for a considerable period we had under observation 2078 cases of the disease. During the epidemic we had a total of 5437 cases under treatment in the hospitals of the Department of Health.

Health officers owe it to the practitioner of medicine to see that every facility is given to study and observe all clinical phases of the disease, and to inform himself as to the possibilities of early and accurate diagnosis and promising or unprofitable methods of treatment.

It is impracticable to allow each patient to be treated by the family physician, and it is undesirable to allow more than the minimum of visits by family or friends. Two visits by members of the family in eight weeks was our rule, and in this way we avoided the development and spread among the patients of the other communicable diseases of children. Complete exclusion of the family would prevent public support of the policy of hospitalization.

Morphological, cultural, and biological tests for the presence of the infecting organism are not yet sufficiently precise or uniform to offer any service to the public health officer. The detection of carriers or of the infectious preparalytic or non-paralytic cases is thus impracticable.

As to general measures of personal restraint directed to the abatement or prevention of an epidemic we are even more at sea than in the field of individual quarantine. As a means of impressing upon the public the seriousness of the epidemic and the need of caution, various measures may be justified, among them the ban upon public assemblages of children within confined spaces, except where medical or nursing supervision and identification of homes or addresses of children could be maintained.

Identification of travelers, especially of children, and their supervision at their place of arrival for the presumed incubation period of the disease is another reasonable means of controlling obvious transmission of the disease; but the incompleteness of this under modern conditions of traffic and in view of the probability of the presence of large numbers of healthy carriers, children and adults, makes its advisability very questionable.

The alternative, one may say, is the absolute quarantine against people coming from places where the disease is prevalent. I hardly need to recall the countless instances of inconvenience, hardship, yes real brutal inhumanity which resulted from the application of the general quarantine of counties, towns, and States against each other during the past summer. I do not know of any health officer who can or has maintained that such measures have had the slightest effect upon the incidence or spread of the disease in his jurisdiction, and I know that nothing has developed so many automobile detours, such ingenuity in the violation of the laws, and such whole-hearted disrespect for reasonable sanitary law and its enforcement.

General reporting by the health officer at the point of departure to the health officer at the place of destination of travelers under the age of sixteen years would probably accomplish all that can be expected. Modern methods of sanitary control are directed toward localizing the disease in the person of the sick individual. Interference with the traveling of healthy people cannot be legally justified, nor will it be cordially supported by the public until health officers can make good their ability to detect and prove the presence of the virus in any one other than those actually suffering or recently recovered from the disease, and in a way that will not materially hinder personal freedom.

In the case of diphtheria, typhoid, cholera, cerebrospinal meningitis, tuberculosis, and malaria carriers we can with but insignificant inconvenience to the individual protect the public by the use of simple and accurate methods of diagnosis.. Furthermore, the rapidity and irregularity of the spread of the disease to other communities develops amazing and laughable inconsistencies in any efforts at local quarantines, as, for example, was the case of quarantines enforced by various communities in New Jersey, Connecticut, and Long Island when the communities outside the city showed a

case incidence in some instances from two to four times as high as that of New York City itself.

If it is admitted that consistent and scientific control of communicable diseases is properly directed to preventing the escape of infectious material from the immediate person or vicinity of the infected individual, and if we can believe the records which indicate that epidemics of poliomyelitis do not occur in schools and institutions as they do commonly in the case of other communicable diseases of childhood, then interference with attendance of children at school is hardly excusable except as a concession to the apprehension of parents. This applies with still greater force to the application of prohibitory regulations to institutions of learning for students of sixteen years or over. The experience in New York City in the public schools and in the City College and other colleges and trade schools fully supports this view.

It is to be deplored that many private schools and colleges adopted regulations calculated to protect their patrons, though with the reasons for their measures based more upon the fears of the parents than upon any probable protective results. The managers of schools and colleges, depending for their income and the support of benefactors upon the good-will of present or prospective students and their parents, may find it good policy to take extraordinary precautions to prevent the invasion of poliomyelitis with the assembling of students for the fall term. One of the results of such additional restrictions has been the development of a feeling often expressed that the children of the poor were but doubtfully protected by the public officers, while the rich received the benefit of a wiser and more conservative policy. Nothing in our experience with the 900,000 public school and parochial school children in New York City gives any support to this point of view.

Uniformity of action among school and college principals in September would have gone far to allay public alarm instead of permitting additional confusion in the public mind and inconveniencing to no good purpose many thousands of families.

Unless there are demonstrable results to be expected from the application of more drastic regulations, those adopted by qualified public health authorities should be accepted and followed by private governing bodies of schools, and colleges, with the approval and advice of their own medical consultants.

Just as interstate uniformity of procedure is advisable under Federal supervision, so intrastate regulations in the several towns, etc., should be as nearly identical as possible.

While awaiting the receipt of the essential information which will justify a logical and efficient administrative control of epidemic poliomyelitis, the health officer of any community can hardly do better than plan his campaign in matters of regulation and public

education in accordance with the declaration of the American Public Health Association, which I take the liberty of quoting in full:

"The specific cause of poliomyelitis is a microörganism, a so-called virus, which may be positively identified at present only by its production of poliomyelitis in monkeys experimentally inoculated. Such experiments have shown this virus to be present not only in the nervous tissues and certain other organs of persons who have died of poliomyelitis, but also in the nose, mouth, and bowel discharges of patients suffering from the disease. It has been proved by similar experiments that healthy associates of poliomyelitis cases may harbor the virus in their noses and throats.

These experiments, together with the fact that monkeys have been infected by direct application of the virus to the mucous membrane of the nose and by feeding of the virus, are strong evidence that in nature infection may be directly spread from person to person.

Observations on the occurrence of the disease might seem at first thought to be inconsistent with this conception, since contact between recognized cases can seldom be traced. However, this may be adequately explained by the lack of means for detecting mild non-paralytic cases, and by the belief that healthy carriers of the virus and undetected cases are considerably more numerous than frankly paralyzed cases.

Many facts, such as the seasonal incidence and rural prevalence of the disease, have seemed to indicate that some insect or animal host, as yet unrecognized, may be a necessary factor in the spread of poliomyelitis, but specific evidence to this effect is lacking, and the weight of present opinion inclines to the view that poliomyelitis is exclusively a human disease and is spread by personal contact, whatever other causes may be found to contribute to its spread. In personal contact we mean to include all the usual opportunities, direct or indirect, immediate or intermediate, for the transference of body discharges from person to person, having in mind as a possibility that the infection may occur through contaminated food.

The incubation period has not been definitely established in human beings. The information at hand indicates that it is less than two weeks, and probably in the great majority of cases, between three and eight days.

If the foregoing conception of the disease is correct, it is obvious that effective preventive measures approaching complete control are impracticable, because isolation of recognized cases of the disease and restraint upon their immediate associates must fail to prevent the spread of infection by unrecognized cases and carriers.

These difficulties would appear to be inherent in the nature of the disease. Nevertheless, we may hope for the development of more thorough knowledge which will permit of more effective control of the disease than is now practicable. Of first importance is the more general recognition by practitioners of non-paralytic cases through clinical observation and laboratory procedures.

Lumbar puncture has been shown to offer valuable aid in diagnosis and a more general use of this test is to be encouraged, since it not only facilitates accurate and early diagnosis, but in many cases affords symptomatic relief as a therapeutic procedure. Without undertaking to predict the future progress of research, we may hope for certain possible developments which may afford far more effective control of the disease, with substantial relief from many inconveniences at present inevitable. Among these possibilities we would include: a practical test for the detection of all clinical types and carriers; a simple and reliable test for distinguishing between susceptible and insusceptible persons; and means of conferring artificial immunity against poliomyelitis.

At present our information demands the employment of the following administrative procedures in attempting to control the disease:

1. The requirement that all recognized and suspected cases be promptly reported.
2. Isolation of patients in screened premises. The duration of infectivity being unknown the period of isolation must necessarily be arbitrary. Six weeks has been recommended by the Conference of State and Territorial Health Officers with the Surgeon-General of the Public Health Service as sufficient, and this period has been generally accepted throughout the United States.
3. Disinfection of all body discharges.
4. Restriction of the movements of intimate associates of the patient so far as practicable. This should include at least exclusion of the children of the family from schools and other gatherings.
5. Protection of children so far as possible from contact with other children or with the general public during epidemics.
6. Observation of contacts for two weeks after the last exposure.

There is no specific treatment of established value in poliomyelitis. During the persistence of the acute symptoms of the disease the important principles of treatment are rest in bed, symptomatic relief, and passive support for the prevention of deformities. Active measures during this stage are not only useless but are apt to cause serious and often permanent injury. Hospitalization of patients when possible is to be encouraged. The best chances of recovery from residual paralysis demand skilful after-care, often long continued, and always under the direction of a physician familiar with the neurological and orthopedic principles of treatment. The provision of such after-care often becomes a community problem,

demanding the coöperation of all available agencies, social and professional."

As a matter of historical interest and to present the result of the experience of the Department of Health of the City of New York, I append the following text of information for field workers which describes the procedure in the various phases of the work undertaken in the effort to check the spread of the disease last summer.

"1. General Information. *Incubation Period.* The incubation period of the disease and the quarantine period of children under sixteen years of age who have been, but no longer are, exposed to infection has been set at fourteen days.

Quarantine. In all families where a case of poliomyelitis has occurred, all the children under sixteen years (except those who have had the disease) are quarantined in the home until two weeks after the termination of the case by death, removal, or recovery. The patient, whether at home or in hospital, is quarantined for eight weeks from the date of onset of the disease. No case in hospital may return home until quarantine is ended.

Placards. All premises where a case of poliomyelitis occurs are placarded, the only exceptions being hotels and boarding houses, which are not placarded provided patient is at once removed to hospital, the room or rooms immediately disinfected, and no quarantined children remain on the premises. In private houses one placard is placed on the street wall of the house and one on the door entering room the patient occupies. In apartment and tenement houses three placards are posted—one on the street wall, one on the wall of the entrance hall, and one on the door of the apartment. All placards must be dated and initialed.

Removal to Hospital. No case may be left at home unless the following conditions are complied with:

(*a*) There must be a physician in daily attendance.

(*b*) The patient must have a special attendant who must obey quarantine regulations and must not do any housework, marketing or perform any household duties for other members of the family. He or she can, however, leave the house provided the necessary precautions as to personal disinfection, etc., are observed, but should avoid all children.

(*c*) The patient and the attendant must have a room, or rooms, separate from the rooms of others in the family.

(*d*) All the windows of this room must be screened and all flies in the room killed.

(*e*) The family must have a separate toilet for its exclusive use.

(*f*) Quarantine regulations must be strictly observed by the patient and the other children of the family, if any. When the

disease occurs in the premises of families of food handlers the employment of such person or persons at this occupation is forbidden, unless they occupy entirely separate apartments for a period of two weeks after the removal, recovery, or death of the patient.

(*g*) Disinfection and renovation: The personal and bed-linen of the patient must be properly disinfected and, after removal, recovery or death of the patient, complete renovation of the room or rooms occupied by the patient and attendant is required.

2. Duties of Inspectors. Cases are reported by physicians, nurses, social workers, and other citizens, and all are visited at once by inspectors, even those reported by physicians, with request that they be admitted to hospital. Attending physicians to Department Hospitals may admit cases direct, without inspector's visits.

The janitor or his representative must be seen in every instance and notified that he or she will be held personally responsible by the Department for keeping quarantined children in the family premises and seeing that placards are not removed or defaced.

If the inspector makes or confirms the diagnosis of poliomyelitis, the Borough Office of the Department is notified and by it the ambulance is summoned, if removal is indicated. In every case the inspector leaves the hospital admission slip, properly and fully filled out. When case is left at home, inspector must give full instructions to family.

All cases of questionable diagnosis must be seen at once in consultation with the Borough or Chief Diagnostician, and whenever it is required, spinal puncture will be made and laboratory report submitted by the staff of the Research Laboratory. Cases with positive laboratory findings will be considered as poliomyelitis, regardless of clinical signs. A full history must be recorded on a special card for each assignment covered by inspectors.

3. Duties of Nurses. Nurses will visit every case reported, to instruct the family regarding quarantine, and every other family in the house:

(*a*) That there is a case of this disease in the house.

(*b*) That the other children of the family in which the disease has occurred will be quarantined, and that should they fail to observe quarantine, that fact should be immediately reported to the Department of Health, when steps will be taken to enforce quarantine by a summons to Court.

(*c*) Regarding home cleanliness, personal hygiene, the danger of infection by flies, and other general measures which should be taken to prevent infection.

(*d*) To report at once to the Department any cases of suspicious illness of children, or any case of poliomyelitis, especially if there is no physician in attendance.

A current history must be kept by the nurse for every case, giving dates of visits, action taken, and date and mode of termination.

Nurses must see the janitor or his representative on first visit, and repeat the instructions given by the inspector.

Patients remaining at home and families with quarantined children are visited daily by the nurse or patrolman for the maintenance of quarantine, and oftener if necessary. After removal, recovery or death of the patient, nurses issue renovation notices, following these up by visits until complied with.

4. Duties of Sanitary Police. These officers visit frequently—daily if necessary—quarantined premises, to enforce quarantine of patient and other children in the family, and to affix or replace placards. They serve summonses when quarantine regulations are violated and appear in Court.

5. Ambulance Surgeons. All cases ordered removed to hospital must be removed by the ambulance surgeon without question, with the following exceptions, in each of which the ambulance surgeon must first obtain telephone authorization from the Resident Physician of his hospital to leave the case at home:

(*a*) When removal would endanger life of child (bulbar cases).

(*b*) When family physician can show that requirements will be met at once (or within twelve hours).

Doubtful and mixed infection cases must be removed by themselves in a separate ambulance.

In every case ambulance surgeons must leave a card with parents, giving name and address of hospital to which patient is taken. If inspector has not left admission slip, surgeon must make out same.

6. Visitors to Hospitals. Each case may be visited twice during its stay in the hospital by a parent or guardian. If child is critically ill the guardian or parent will be notified and will be permitted to visit daily while child is dangerously ill. Information relative to condition is given out at the Information Desk in each hospital, or by telephone in response to telephone inquiry from the parent or guardian.

7. Certificates for Children Leaving the City. The Department of Health of New York City does not require certificates of anyone leaving or entering the city. It issues certificates only as a convenience and aid to persons leaving the city. None are issued to persons passing through the city.

Such certificates state that the persons or family therein named have not resided in a house where a case of poliomyelitis has occurred. The applicant must sign a request for the certificate. They are refused to persons who live in a house where a case of infantile paralysis has occurred or who present symptoms of the said disease.

The certificates are good only until midnight of the following

day, except when issued on a Saturaday or on the day preceding a holiday, when they are good until midnight of the second following day.

Persons Leaving New York State. Officers of the U. S. Public Health Service, stationed at transportation terminals, require the above certificates before they will permit children under fifteen years of age, resident in New York City, traveling to points outside the State of New York, to leave the city. The original applicant must again sign the certificate in the presence of the Federal Health Officer. Federal Health Officers do not require certificates of any adults.

Persons Going to Points within New York State. Residents of New York City, adults or children, traveling to points within New York State, who present certificates of good health from their family physicians, may also obtain the above certificates from the Department of Health. If no physician's certificate of good health is presented, applicants will be examined by a physician and their freedom from symptoms of poliomyelitis certified; in this case all children must be brought to the proper office of the Department.

8. Return of Cases of Poliomyelitis to New York City. Cases of poliomyelitis occurring in residents of New York City who are temporarily residing outside the city, and developing within two weeks of the time of leaving the city, will be permitted to return, provided (*a*) a private conveyance (private car, private automobile, carriage or ambulance) is used, and (*b*) the patient goes direct to a hospital authorized by the Department of Health to care for cases of poliomyelitis.

Cases in which the onset of the disease occurs two weeks or more after leaving the city, may not return to New York City until eight weeks from the date of onset of the disease. But in special cases, where proper medical, surgical and nursing care is not obtainable, patients may be brought back to the city in a private conveyance, providing they go directly to a private room in a private hospital authorized by the Department of Health to receive cases of poliomyelitis.

9. Return of Children Who Have Been Exposed to Poliomyelitis to New York City. Children under sixteen outside of New York City who have been exposed to infection with poliomyelitis within two weeks, may return to the city under the following conditions:

They must come by private conveyance and must go direct to their homes.

Advance notice must be sent, and authorization obtained, by telephone, by the local Health Officer. Such notice must give the name and age of each child, together with the identified address,

including the floor, and the latest date of exposure to infection, and must be followed immediately by a written notice.

Such children will be promptly visited at their homes by a representative of the Department of Health, and instructed as to nature and duration of quarantine. They must not leave the premises until two weeks have elapsed from the date of last exposure to infection.

The premises are not placarded, but the children are visited at regular intervals, and should quarantine be violated the parents or guardians are summoned to Court and fined."

POLIOMYELITIS: THE PREPARALYTIC STAGE AND DIAGNOSIS.

By John Ruhräh, M.D.,
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To anyone who has passed through one or more epidemics of poliomyelitis, or who has become thoroughly conversant with the disease through reading, the following pages will be of only passing interest; but I am convinced from my association with other physicians, particularly in seeing cases of the disease, that an article dealing with the preparalytic stage, with the findings in the cerebrospinal fluid, and a few points on the differential diagnosis will be welcomed by many. The old idea of the disease and its clinical paralytic form has become fixed in the minds of the medical profession, so that it will need repeated contributions to eradicate these earlier conceptions of it. I have had, during the past six months, a rather unusual opportunity of seeing a large number of cases, and it was with pleasure that I responded to the invitation of the editor to prepare the following pages.

The Abortive Form and Preparalytic Stage. Wickman, in his marvelous monograph, divides the abortive cases into four classes:

1. Those with the course of a general infection.
2. Those showing meningeal irritation.
3. Those with marked pains suggesting an influenza.
4. Those with accompanying gastro-intestinal disturbances.

To this one might add a fifth, for the purpose of calling attention to it, of an anginal form, or those beginning with definite sore throat.

It should be borne in mind that poliomyelitis is a disease which, probably in a very large proportion of cases, does not involve the nervous system to such an extent as to cause special symptoms, and the cases characterized as abortive are merely those which go through a preparalytic stage without having any definite paralysis following. If this point is borne in mind it simplifies the conception

and also the description of these cases, for what is true of the abortive cases is equally true of the preparalytic stage of the ordinary form of the disease. Doubtless a great number of the so-called abortive cases have muscular weakness or even paralysis of a very limited amount. It is extremely difficult to detect even marked difference in muscular power in very young infants, so that the lesser degrees of loss of power may easily escape notice even after the most searching and repeated examinations.

The onset of the disease is usually sudden. Occasionally the onset is gradual and it may not be possible to tell exactly when the child was taken ill. The severity of the initial symptoms bears no relation whatever to the subsequent course of the disease, as one sees a very mild onset followed by most extensive paralysis and even death, and other cases coming in a most fulminating manner which subsequently clear up entirely. The first thing observed about the child is that it is ill, and of all the symptoms noted fever is the most constant. There are, perhaps, exceptional cases in which the febrile stage is slight and short and so easily overlooked by ignorant or careless parents; but in cases under careful observation the afebrile attacks are certainly most exceptional. The second most notable symptom is the presence of pain, and in children old enough to locate the pain, headache is, next to fever, the commonest symptom. The pains may be in any part of the body and may be so marked as to overshadow all other features of the disease, or they may be so trifling as to be only elicited by special examination, with all gradations in between. The commonest pain next to headache, and of decidedly more value in diagnosis, is a tenderness and pain along the spine and down the legs reaching to the heels or even the soles of the feet, and another very common and suggestive pain is that in the neck and back of the head. If the head is bent forward this is usually greatly increased, causing the child to cry out and resist very markedly. If there is not much pain present it can usually be elicited by bending the legs up and the head forward, so as to flex the spine. In some children the pain is present only when one attempts to move the arms or legs or various parts of the body; in others it is spontaneous and the child cries most of the time with it; and in still others there is a hyperesthesia, so that the slightest touch without any movement whatever elicits an unusual degree of suffering. In some cases pain is elicited on gently squeezing the muscles. In many cases there is slight stiffness of the neck and the child assumes a very suggestive attitude, lying on one side or the other, but not on the back, so that the head may be thrown slightly backward. The legs are usually drawn up, although not always. The disease may be ushered in with a convulsion, or convulsions may occur in the course of the disease.

The mental condition is extremely interesting. The commonest form of disturbance consists of very marked drowsiness, which is

replaced by a most extraordinary irritability when the child is aroused; but when one ceases to examine him he rolls over into his former position and dozes off again. Other children are extremely restless and irritable and some are wideawake with a hyperacute mentality. With this is a very evident delirium or a tendency to delirium. These cases, in my experience, are of the worst possible type and usually die. In some children there is a very marked delirium—talking, muttering—and this is accompanied by a tendency to move about in the bed and change the position frequently. Often the moving about is exceedingly suggestive, the child tossing from side to side and not lying in any position more than a few moments, sitting up, standing up, and half turning from side to side in a perfectly purposeless way. If the child is watched carefully it will very often be seen to have fibrillary twitching of the muscles; at other times whole muscles will tremble. In rare instances the muscle is more or less spastic and may stiffen when the extremity is taken hold of to relax a few moments later.

The gastro-intestinal symptoms are not uncommon. Anorexia is the rule. Vomiting may be present and may be so marked as to suggest an acidosis. Constipation is rather more common than diarrhea, but the latter is frequently met with. The throat is often reddened; the redness is general and not limited to the tonsils, and in some cases there is a considerable amount of coryza and slight suffusion of the eyes. Another curious feature met with both early and later on in the disease is the tendency to profuse sweating. This may be as marked as the colliquative sweats seen in typhoid. Sometimes the sweating is limited to one part of the body, as to the face or neck, or to one extremity, sometimes to one-half of the face. In some cases there may be retention of the urine, and this should always be looked for.

Usually, as Wickman has suggested, the disease presents certain dominant features. The cases which are like the course of a general infection have nothing to suggest the diagnosis, or they may have some of the things mentioned above, the general history of the attack being that the child is taken ill suddenly with an attack of vomiting followed by a fever of from 101° to 103° or 104°, or sometimes higher, with headache, and feeling very badly, but without any definite symptoms of any kind. This may clear up in twenty-four hours, or it may last two, three, or rarely four days, when the symptoms disappear entirely and the child has nothing whatever to show for it. These cases may be seen in connection with two or three or more cases in a family or group of children, and the diagnosis is made or suspected by the fact that the child was taken ill at the same time with identical symptoms or nearly so, to one or more definite cases of the disease in the immediate surroundings. These cases present the greatest difficulty in diagnosis.

The meningeal form is the most suggestive of all, and one almost

immediately realizes that he has either to do with a beginning poliomyelitis, a meningitis, or a meningismus. In these cases, when the patient is examined, it will be found there is an anterior and posterior stiffness of the neck; Kernig's sign may be present or absent; McEwen's sign elicited by percussing and auscultating the cranium may be present, owing to the distention of the ventricles of the brain with the fluid; and the patient may show a very characteristic sign at this time, or usually a little later, which may be described as follows: If the patient is raised by placing the hands under the shoulders the head will fall back. If the child is told to raise the head when it is sufficiently conscious, it will do so and hold it forward a moment or so and the head will again fall back. This is a sign of very great importance. In some cases there is a curious vasomotor disturbance which is most often seen in the cases of the meningeal form. This consists of an alternate blushing and paling of various areas of the skin. It may be over small spots or over large areas, the part affected being redder than normal, and then after a varying time it may become paler than the surrounding skin or present a normal appearance. Sometimes the flushing is very transient and is only a momentary wavering flooding of the superficial vessels. There is practically never any question in these cases with a meningeal irritability of the advisability of a lumbar puncture, and it should be done as soon as possible, and this usually clears up the diagnosis immediately. The cases with marked pain, resembling influenza, should suggest poliomyelitis. In my own experience I have rarely seen cases of influenza with as much pain, or with the kind of pain, as described above, although they do occur. In these cases a lumbar puncture should be done to settle the question of diagnosis.

The gastro-intestinal cases are more difficult because one does not always have in mind the possibility of a poliomyelitis. The child is taken with a fever with intense vomiting, and if it has had a history of acidosis with vomiting before this the physician may be thrown off his guard. In some of these cases, if the child is carefully observed, some of the special features mentioned above may be elicited, but if they are absent the diagnosis may be impossible. The presence of a very marked diacetic acid reaction in the urine will incline one to believe that the case is one of acidosis, though it must be borne in mind that any febrile condition will show diacetic acid in the urine, although the reaction is not as marked.

The cases with sore throat and coryza are also difficult and practically impossible to tell unless a careful examination elicits some suggestive symptoms or signs. This preparalytic stage, when it does not go on to the development of a paralysis, is what we have called an abortive case, and may subside in twenty-four hours, or it may last two, three, or four days, occasionally five, six, seven, or eight days; in a few instances longer, but rarely. In some of

these cases the convalescence may be slow and the child may suffer with indefinite symptoms for days or even weeks after the attack. These consist chiefly of pain coming on at any time, but more often at night, sometimes waking the child up out of sleep. These pains are usually transient and disappear either spontaneously or after rubbing the affected parts. In some instances the pain is accompanied with cramps in the muscles. The child may tire readily on exertion even though it has shown no paralysis or loss of power, or the tiring may be localized to certain groups of muscles or to one extremity. When this is the case one might assume that the spinal cells supplying this part have been affected. If the child is old enough to make special tests of the power of the muscles according to the method suggested by Lovett the diagnosis may be even more certain.

The Cerebrospinal Fluid. The cerebrospinal fluid in practically all cases, certainly in almost all if not all of the cases which show nervous symptoms, is abnormal and may present a number of different changes which, in the main, are constant. The fluid is sterile, usually clear, and sometimes a slight fibrin web forms in it. In exceptional cases the fluid may be cloudy or even bloody. Usually the presence of blood means a faulty technic, the error generally being the use of a needle without a sufficiently close-fitting obturator. The number of cells is definitely increased. The normal fluid contains from five to ten cells per cubic millimeter, while in poliomyelitis the number of cells is increased from sixteen to twenty to one hundred, but in some instances this number is greatly exceeded, as high as five hundred or over being met with. In the early stage of the disease, before the paralysis has made appearance, the chief type of cell found is the polymorphonuclear. Sometimes they form from 80 to 90 per cent. of the cells present. After the appearance of the paralysis the cells found are chiefly lymphocytes, and from 75 to 100 per cent. of the cells present are of the mononuclear type. There is also the presence of large mononuclear cells of an endothelial type which have been regarded by DuBois and Neal as rather characteristic of poliomyelitis. There are also phagocytic cells present. It must be borne in mind that even a slight admixture of blood will account for a certain number of polynuclear cells. The cells rapidly disappear from the cerebrospinal fluid, so that after the first two weeks the count is either normal or nearly so. The fluid is sterile, gives a positive Fehling's reaction like the normal fluid, and usually contains a very definite reaction for globulin, which is, however, not as pronounced as that found in the various forms of meningitis. During the first week the globulin is found in perhaps one-half of the fluids examined. Pandy's test will, as a rule, be found easy and reliable. The globulin increases, as a rule, until about the third week, when it decreases, but a slight increase may be detected even after seven weeks or longer. The

reaction to Fehling's solution is of slight value in diagnosis, inasmuch as in tuberculous meningitis, and sometimes in meningitis due to other organisms, this power to reduce Fehling's solution is absent. If the reaction is present it means nothing, if it is absent it is a point against poliomyelitis.

The fluid in meningismus is increased from 10 to 100 c.c., is sterile, clear, and contains very few cells. Albumin and globulin may be present in very slight traces, or may be absent, the reaction never being anything approaching that seen in poliomyelitis. The Fehling's solution is reduced and animals inoculated with the fluid gave negative results. In tuberculous meningitis, which may resemble poliomyelitis closely, the fluid is usually markedly increased from 30 to 120 c.c. or more, and is usually under decided pressure. On standing a clear fibrin web usually forms, and this is much more marked than the slight web sometimes seen in poliomyelitis; in practically no other fluid is such a dense web seen. This contains a great many cells, and after transfer to a slide and stained, tubercle bacilli may usually be demonstrated if a sufficient amount of time is given to the search. I do not remember a case of tuberculous meningitis which I have seen in recent years in which the tubercle bacillus could not be demonstrated, although sometimes it took a considerable time to do it. The cells present are lymphocytes, which form about 95 per cent. or more of those seen. The reaction for albumin and globulin are more marked, very much more marked than the reaction seen in poliomyelitis. In about 25 per cent. of the cases Fehling's solution is not reduced. Animal inoculations (guinea-pigs) show tuberculosis in about four weeks' time.

In cerebrospinal fever the pressure of the fluid is definitely increased, and the amount very much, as in tuberculous meningitis. The fluid is turbid or cloudy, and stained specimens show the presence of the meningococcus. The cells present are polymorphonuclears up to 98 per cent. The albumin and globulin reactions are as in tuberculous meningitis, and Fehling's solution may or may not be reduced. In meningitis due to other organisms the fluid is increased, is turbid or cloudy, and otherwise resembles that of cerebrospinal fever except that the organism demonstrated in the smears will be found to be a pneumococcus or influenza bacillus or whatever happens to be the cause of the inflammation.

Diagnosis. The diagnosis of poliomyelitis presents certain difficulties, the commonest of which are in the cases in the preparalytic stage. If it is borne in mind that the disease may be regarded as a general infection and that various parts of the body may be affected, one understands more readily the rather protean symptomatology of the disease. At the present time the most important thing to confirm the diagnosis is the examination of the cerebrospinal fluid, and abortive cases showing a normal fluid must therefore remain more or less doubtful. The question of whether the child may have

poliomyelitis without having any changes in the cerebrospinal fluid is at present an open one. The general rule is if a case shows a normal spinal fluid that it is not to be regarded as poliomyelitis. Usually when there are any symptoms whatever of involvement of the nervous system the case turns out to be one of poliomyelitis. One sees a patient occasionally, particularly in association with other cases in the same family, in which the cerebrospinal fluid is normal, but in which the patient was strongly suspected of having the disease. This point might possibly be cleared up by a series of observations upon animals.

Another method of diagnosis which has been employed, but which is not suited for ordinary use, is to take the serum from the suspected case, mix it with a fatal dose of the virus, and after incubating it inject it intracerebrally into monkeys. A failure to develop the disease would indicate that the virus had been neutralized, but it must be borne in mind that serum from persons having had the disease recently will also neutralize the fluid, and if the individual had passed through an unrecognized abortive attack the results could well be misleading.

The diagnosis of the paralysis itself is not always easy. In older children it is usually apparent and the child will tell you he cannot make certain movements if asked to do so, unless he is too ill to take notice. In the very sick and the very young the production of pain or tickling must be used and the unparalyzed member will be used to protect the paralyzed one or to brush away the source of the irritation. In young babies picking up the child with the hands under the shoulders and buttocks, leaving the limbs free, will usually make the paralyzed parts plain. The normal infant moves all its members, in the paralyzed the affected part hangs in marked contrast with the moving arms or legs. In very ill children this is not as effective, but still of value.

Before the onset of the paralysis, or when it is unrecognized, the case may be mistaken for almost any acute febrile disturbance, and great care should be taken to elicit changes in the nervous system. In the presence of an epidemic even comparatively slight changes may be sufficient evidence on which to do a lumbar puncture, and most parents will welcome any method which abridges their suspense. The most common sources of error, apart from conditions with nervous symptoms, are as follows:

Croup or Laryngitis. With a paralysis of the laryngeal muscles the case may present such dyspnea as to require intubation and the child may be suspected of having croup, laryngitis, or laryngeal diphtheria. Other paralyses will generally be found on careful examination and the absence of any other evidence of diphtheria will generally make the case clear.

Bronchopneumonia. A child with a paralysis of the respiratory muscles may suggest a pneumonia. On careful examination either

the thoracic muscles or the diaphragm will be found paralyzed. The fixed chest wall, either one or both sides with exaggerated abdominal breathing, characterizes the first. When the diaphragm is paralyzed, instead of inspiratory distention of the abdomen there is an inspiratory retraction. With hurried respiration and a little bronchitis or pulmonary edema the physical signs may be misleading unless one is unusually skilled, and even then.

Nephritis with Uremia. This may be misleading on account of the convulsions or coma. The edema and urinary findings will be sufficient to clear up the diagnosis, or a lumbar puncture may be done.

Acidosis. Cyclic Vomiting. This may be very misleading. The profound languor may suggest a generalized slight loss of power, such as is sometimes seen. There may be twitching of the muscles and other nervous symptoms. The acetone odor of the breath and the marked diacetic reaction in the urine will point the way. The reaction in ordinary febrile disturbances is rarely as pronounced as in acidosis. A lumbar puncture may be needed.

Diarrhea. When the symptoms of gastro-intestinal disturbances are very marked the diagnosis may not even be suspected, inasmuch as meningismus and other nervous symptoms are not uncommon in connection with diarrhea. The lumbar puncture will afford a means of settling the question in suspected cases.

One should bear in mind that poliomyelitis may coexist with other diseases and with injuries. A surgeon recently told me of a case occurring in a boy with a broken arm. A couple of weeks after the arm had been put up it became very painful, and there was a slight fever. It turned out to be a poliomyelitis. The disease complicating medical conditions is readily imagined and needs no further detail.

A second class of disease in which there is pseudoparalysis or spasm may also cause difficulty in diagnosis. This includes scurvy, rickets, hysteria, the spasmophilia seen in nutritional disturbances, and tetany.

Scurvy. In severe scurvy the child assumes a position which suggests poliomyelitis. The paralysis is only apparent and the child can be made to move the extremities if sufficiently irritated. In the very late cases the muscles will be seen to move if the limbs do not. The reflexes are normal. There are, in addition, the classic signs, the bleeding of the gums, the submucous and subdermal hemorrhages, the periosteal swellings, etc., and symptoms rapidly disappear on the administration of orange juice.

Rickets. In acute rickets there is a pseudoparalysis like that described in scurvy, but in place of the scorbutic symptoms there are marked evidences of rickets.

Tetany. The characteristic position, the spasm being chiefly in the hands and feet and bilateral, the exaggerated reflexes, the

contraction of the muscles on percussing the nerve, best seen in the facial, and the spasm caused by constricting a limb make the diagnosis easy.

Spasmophilia. Apart from tetany a definite tendency to contraction of the muscles exists in certain poorly nourished young infants. The reflexes are increased and the stiffness of the muscles is general.

Hysteria. This may present some real difficulties. Fortunately it is rare in older and practically absent in young children. The reflexes are normal and there are sensory disturbances, usually anesthesia of the glove and stocking type. If the condition has existed for some time the absence of marked atrophy is of value.

The third class of cases includes those in which there is some definite disease of the nervous system. To avoid repetition *let me insist upon the necessity of obtaining the history of the attack.* This will save many embarrassments and will also eliminate the congenital conditions. The history may be impossible or difficult to get or may be misleading, but usually it will help tremendously.

In this connection one must bear in mind the possibility of encountering an old poliomyelitis with some intercurrent fever added. We are dealing only with the diagnosis in the acute stage or near it, so that the differential diagnosis between the old nervous lesions will not be touched on.

In the following diseases *the examination of the cerebrospinal fluid is the deciding point.*

Tuberculous Meningitis. This may give more difficulty than any other condition. The general appearance, as a rule, is different, but this may not mean much until the child has been seen several times. The cerebrospinal fluid is under greater pressure than in poliomyelitis. Sooner or later there are changes in the eye-grounds. The onset is more slow and more irregular. The dominant symptoms are drowsiness, vomiting, irregular pulse and respiration, convulsions, and rigidity of the muscles. The reflexes are increased. In poliomyelitis the length of time to reach the same stage is much more brief, and while in the incubation stage there may be rigidity or increased reflexes the tendency is to become flaccid and to have a loss of reflexes.

Cerebrospinal Fever. At the onset the two diseases may be strikingly alike. The sudden onset with vomiting and high fever, the prostration and rigidity of neck and extremities, the drowsiness with irritability and hyperesthesia, may be simulated by poliomyelitis. The petechial eruption, if present, is a help, and after a few days the marked spasticity and increased reflexes give a picture usually easy to distinguish.

Other Forms of Meningitis. Much as above, the diagnosis depending on finding the causal organisms in the cerebrospinal fluid.

Meningismus. Meningeal symptoms, drowsiness, retraction of the head, etc., may be seen in connection with inflammatory diseases

of the body elsewhere, as in pneumonia and enterocolitis. This may be intensified by a great loss of fluid from the body, as in the last-named disease. These conditions may tax the diagnostic powers if only the symptoms and physical signs are depended upon. The recognition of the existing disease and the cerebrospinal fluid clear up any doubts.

Cerebral Thrombosis. This is seen in connection with inflammatory diseases elsewhere in the body, and the diagnosis may not be suspected. If symptoms are produced that stand out above those of the causative condition they are convulsions and paralysis, either localized or general, strabismus, and coma. When the disease extends from a neighboring inflammation, as in the nose or ear, the symptoms may be more marked, and consist of headache, drowsiness, and if pyemia occurs, chills, sweats, and a high variable temperature. I have seen one instance of a lateral sinus thrombosis in which the drowsiness and irritability were not unsuggestive of poliomyelitis. The localizing symptoms, cyanosis of the face with dilatation of the temporal and frontal veins in thrombosis of the longitudinal sinus, the marked edema of eyelids and face and protrusion of the eye in cavernous thrombosis, and the extension into the neck in lateral sinus trouble soon make the diagnosis plain.

Mental Deficiency. When there is some febrile disturbance this has more than once been mistaken for poliomyelitis. The history, if obtainable, and the subsequent history, if not, will generally make the question clear, and one can always resort to a lumbar puncture. I have seen some extraordinary clinical pictures when the two were associated.

Amaurotic Family Idiocy. Tay-Sachs's Disease. This, too, can be mistaken if there is an intercurrent fever, as the flaccidity suggests poliomyelitis. The condition affects all the muscles, the blindness is apparent, and there are characteristic changes in the eye-grounds. It occurs in Jews, and the history of gradual onset, beginning between the third and sixth month, is usually obtainable.

Transverse Myelitis. This may occur in connection with the acute infectious diseases. The increased reflexes below the lesion and the involvement of bladder and bowels ought to make the diagnosis easy.

Pott's Disease. By pressure this may cause a paralysis with increased reflexes. The diagnosis is usually apparent, but cases have been sent to hospitals as poliomyelitis.

Congenital Spastic Paralysis. Despite the fact that these do not resemble acute poliomyelitis they have been mistaken for it. The differential diagnosis of late poliomyelitis and these cases is another story.

Chorea. This disease has also been mistaken for poliomyelitis, but ordinary careful examination ought to solve the difficulty.

Facial Paralysis. Bell's Palsy. In times of epidemic this may give considerable difficulty. In doubtful cases the only way to

clear up the diagnosis is by lumbar puncture, but a facial paralysis coming on after definite exposure to cold and preceded by earache is apt to be called Bell's palsy, and the same is true of cases in which there is marked involvement of the ear. On the other hand, a case coming on with a history similar to poliomyelitis can fairly safely be classed as that disease.

Peripheral Neuritis. Cases of this disease may cause very distinct difficulties in diagnosis. In children it usually follows an infectious disease. It is most common after diphtheria, and there is usually a history of throat involvement. The most common forms of paralysis are those of the soft palate and of the eye muscles, particularly of the accommodation. The patient often shows irregular heart action with dilatation of the heart. In poliomyelitis the paralysis comes on within a few days, usually within the first eight days. In diphtheritic paralysis the onset is later. In Rolleston's series, on which I commented in *Progressive Medicine* for March, 1914, the only forms of paralysis which occurred during the first two weeks were those involving the palate and the so-called cardiac paralysis. The ocular paralyses are more apt to occur during the fourth and fifth week, although some occur in the third week, and paralysis involving the lips, pharynx, or diaphragm almost always occurs later than this, that is, during the sixth, seventh, and eighth week. In cases seen early a lumbar puncture will settle the question, but in cases occurring late in which no history can be obtained the difficulties of diagnosis may be almost insurmountable.

THE CLINICAL ASPECTS AND TREATMENT OF ACUTE POLIOMYELITIS.

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The epidemic of acute poliomyelitis occurring during 1916 has produced an infinitely larger number of cases than during any preceding epidemic. Up to December 1, 1916, there were 999 cases in Philadelphia, 768 of which were treated at the Philadelphia Hospital for Contagious Diseases, and it is mainly upon the study of these latter that this paper is based.

It has been brought out very forcibly that, while belonging to the acute infectious diseases, it is a general disease in which almost all the organs of the body are involved. This has been proved conclusively by postmortem findings and by experimental work, showing that a solution made from these organs when injected into monkeys has caused typical acute poliomyelitis, which strengthens our belief that the principal mode of entrance in the human being

is through the gastro-intestinal tract. The organs in which the most marked lesions are found are the gastro-intestinal tract, liver, spleen, lymphatic glands, and lungs in addition to the well-known changes in the spinal cord. It is important for us to recognize these facts early, as they assist materially in making a diagnosis during the preparalytic stage. The older writers have laid much stress upon the natural immunity which most children possess. This apparently has either decreased to a great extent or, what is more likely, the disease has not been recognized in large numbers of children who have had it only in the preparalytic stage, or, in other words, have had the general symptoms without the special spinal manifestations. The surroundings and general condition of children seem to play an unimportant part in this disease, as the best cared for and healthiest children suffer quite as frequently as those living under the poorest hygienic surroundings in the most overcrowded parts of the community. While it is distinctly a disease of early childhood, over 80 per cent. of cases occurring under five years of age, it is found with diminishing frequency up to sixteen years, after which age about 1.5 per cent. of cases occur.

During the time elapsing from the appearance of the first symptom until paralysis occurs there are many important and interesting facts to be discovered; in the first place the duration of the preparalytic stage varies from twenty-four hours to twelve days. In the larger number, however, the first signs of paralysis develop during the first or second day. Invariably the first symptom noticed by the parents has been the presence of fever, ranging from 102° F. to 105° F.; the temperature, while not remaining so elevated, continues above normal for from seven to ten days, or, in other words, into the paralytic stage, both pulse and respiration being markedly increased, and as the temperature lessens they still remain much above normal, the pulse varying from 120 to 160 and the respirations from 30 to 60. Constipation is the next symptom most frequently present, and while, as a rule, it is only slight in character, it indicates an intestinal derangement. In older children this is frequently accompanied by abdominal pain, at times so severe and so localized that appendicitis has been diagnosed. Vomiting as an early symptom occurs only less frequently than constipation, and in older children is associated with nausea and headache. In a very small percentage of cases a slight diarrhea has been noticed, while in only two cases was a severe enteritis present during this period. Irritability and restlessness or fretfulness often occur, while drowsiness or even stupor appears in a moderately large number. These cases, however, are easily aroused, and if old enough will answer questions intelligently. In the rachitic type of child we find a few in which convulsions occur, but even here not with the frequency to be expected in a disease causing so much general and local disturbance. Pain and rigidity in the muscles of the neck are noted in over half of the cases. This is seen on bending the child's head

forward. It may be present from the first day or may not develop until just before the onset of other paralyses. An interesting and suggestive symptom seen occasionally, but not with great frequency, is that of muscle tremor. This may be local or general, in some cases the entire body showing the effect of this condition. As a rule, one finds the patellar reflex either lost or greatly diminished during the preparalytic stage, while in a few instances exaggeration of the patellar reflex has been found.

The severity of the symptoms at this time has apparently no bearing upon the degree or extent of the ensuing paralysis.

In the abortive type of cases, or those which never pass beyond the preparalytic stage, we frequently find extremely severe symptoms; that is to say, they will run a temperature of the highest type, ranging from 104° F. to 105° F., while the pulse-rate will be between 140 and 180, the respirations from 50 to 80, vomiting more acute and frequent in occurrence, while the constipation is marked, in some cases even leading one to suspect intestinal obstruction. Of course, there are many others of this same type who do not show such a marked clinical picture, giving only a slight rise in temperature, not over 101° F., but the pulse will invariably be much increased, 120 to 140, and respirations between 30 and 40. These cases will, as a rule, clear up within four to six days, leaving no paralysis or weakness of any set of muscles, and if it were not for the diagnostic aid of the lumbar puncture and the cell count therefrom many cases would not be correctly diagnosed. In fact, we feel assured that hundreds of such abortive cases have occurred not only in our city but wherever the epidemic has been in progress.

Case I.—*Typical Abortive Case.*

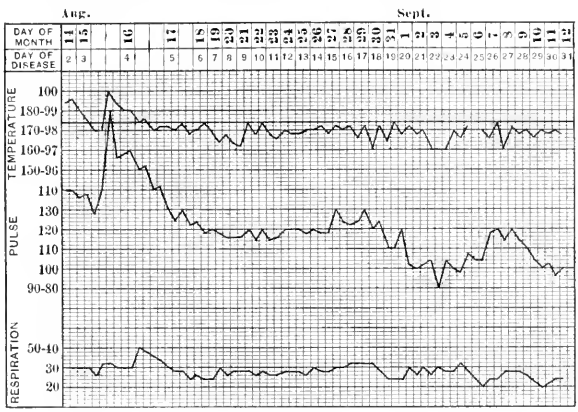
J. R. S.; male; aged five years. Seen in consultation with Dr. Elmer, of Wayne, October 2, 1916. Two days previously the child had abdominal pain and slight constipation. On the morning of October 1 the temperature was 103.4° F., pulse 144. In the evening of the same day the temperature was 105.8° F. The child complained of headache, was very quiet, and slept most of the time. The next morning he was stuporous, though answered questions when aroused. Temperature at that time was 105° F., pulse 144, respirations 42. There was rigidity of the neck, with pain on nodding motion. When seen at 11.30 P.M. the temperature was 101.8° F., pulse 140, and respirations 40. The knee-jerks were normal at 5.30 P.M., left knee-jerk absent at midnight. Right plantar was sluggish, Babinski on left, Kernig present on both sides. Lumbar puncture removed 37 c.c. of clear spinal fluid under greatly increased pressure, the cell count being 167 per cm. One-half cubic centimeter of adrenalin chloride was injected into the spinal canal.

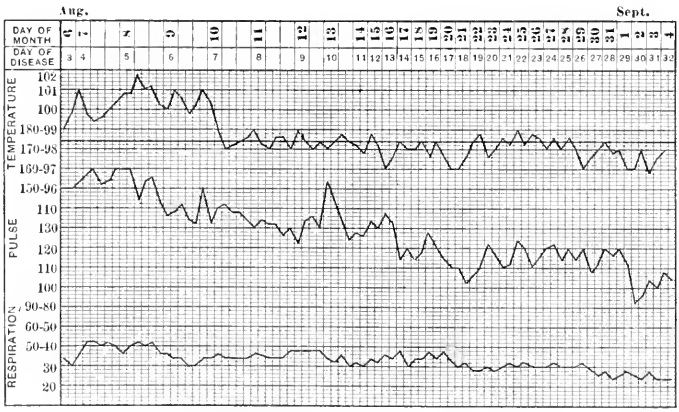
October 3. Improvement was marked. Temperature was normal; free action of both legs and knee-jerks were present. He was reported to have made an uneventful recovery without paralysis.

This case is peculiarly interesting, owing to the fact that ten days

previously a younger child developed similar symptoms with complete recovery within a few days.

It is difficult to define the length of the acute paralytic stage, as it varies so greatly in different individuals. The temperature, as a rule, becomes normal either with the onset of paralysis, or at least does not remain more than a degree elevated for two or three days, after which time it almost invariably runs a subnormal course for from one to three weeks. It seems that more reliance





must be put upon the clinical picture of the pulse and respiration in reaching some definite conclusion regarding the duration of the acute paralytic stage. We find that while there is a moderate variation in pulse and respiration it is rare to find both having reached normal within three weeks from the date of onset, while many will still show an increased rate up to five and six weeks, others having been removed from the hospital before the return to normal. The above charts show the typical course of the temperature, pulse, and respiration.

Pain is one of the conditions found with moderate frequency during this stage. It is especially referable to the hip-joint, and in the majority of cases is only present on motion; that is to say, when the child is lying quietly there is no pain, but as soon as the leg is moved the child cries out. In other cases pain may be referred to any of the affected parts, especially the shoulders, elbows, and back. Its duration is exceedingly variable; in some cases following lumbar puncture it disappears and does not return; in others it is relieved by lumbar puncture but returns within a few hours or days.

In other cases it may not be present for weeks, when suddenly pain and more or less weakness of the affected part are complained of. We have found that if lumbar puncture is immediately done the pain will be relieved in 90 per cent. of these cases.

As a rule the appetite of these children is unimpaired, though the power of digestion and assimilation are distinctly below par, and for that reason great care must be taken of their diet. Constipation is the rule and laxatives must be used with greater frequency than in other diseases.

While a study of the parts involved would be of much interest it is not possible to more than glance at a few of the important combinations. In 25 per cent. of all cases the legs, either one or both, were the only parts involved; in 12 per cent. the arms only, one or both, were affected; in only 4 per cent. was a true crossed paralysis found. Other combinations, including the face, eyes, neck, back, chest, abdomen, bladder, deglutition, and vocal cords, are so numerous and varied that it is impossible to include them in this paper. In only 2 per cent. of the cases have we found the bladder to have been involved. It usually occurred between the second and fifth day of the paralysis, and lasts, as a rule, for from a few hours to forty-eight hours. Older children complained of pain from the distended bladder, while in the younger children it was only found on examination. This condition cleared up rapidly, usually without catheterization, and without leaving any cystitis.

In many of the severe cases which were brought to the hospital on the first or second day of the acute paralytic stage, progressive paralysis was noted, some presenting the typical picture of ascending or Landry's paralysis; others progressed in an extremely irregular manner, this latter form being the most common. Some cases progressed with such rapidity that within twelve hours all extremities —neck, back, chest, and abdomen—were involved, death resulting within a few hours or in from one to three days. Others were much slower, the period of progression lasting six to seven days.

Case II.—*Progressive Paralysis.*

E. B.; male; aged two years. Admitted to hospital September 2, 1916 with the following history: Illness began August 30, with fever, backache, and constipation. Paralysis developed August 31. Examination showed rigidity of the neck; good chest expan-

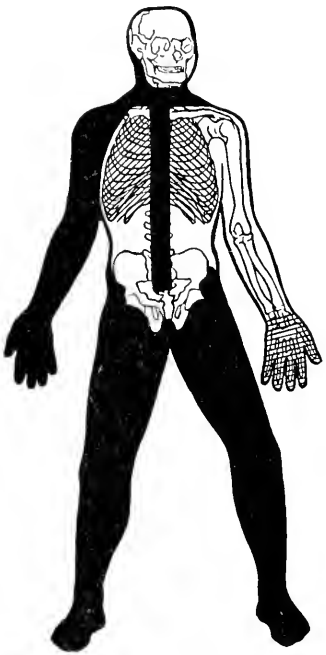
sion; arms normal; complete paralysis of both lets; knee-jerks absent; plantar reflexes sluggish. Lumbar puncture gave 20 c.c. of clear fluid; cell count, 110 per cm.

September 3. There was complete paralysis of the vocal cords.

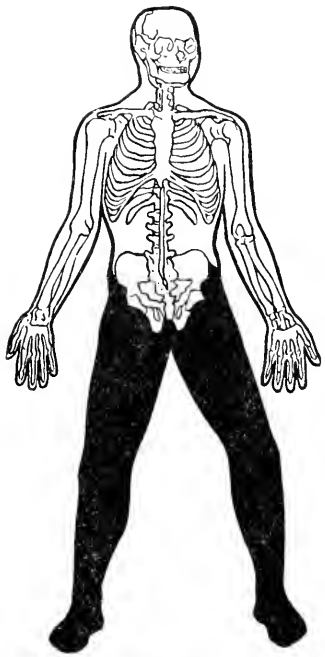
September 4. There was paralysis of the muscles of the back and of the right arm, with weakness of the left hand; 15 c.c. of immune serum was given intraspinally following lumbar puncture.

September 5. Ten cubic centimeters of immune serum was given intravenously.

September 6. Chest expansion limited. Lumbar puncture gave 20 c.c. clear fluid; 10 c.c. immune serum was given intraspinally.



CASE II.—E. B. Height of paralysis.



CASE II.—E. B. On discharge.

September 7. Paralysis of vocal cords had disappeared.

September 11. General condition was very much improved; rigidity of neck and back had disappeared.

September 14. Chest expansion was normal.

September 21. It was noted that his condition was still very weak and there had been no change in the paralysis since September 14.

September 23. Eighteen cubic centimeters of clear fluid was removed by lumbar puncture under moderate pressure.

September 24. Twenty-five cubic centimeters of clear fluid was removed by lumbar puncture under increased pressure.

September 25. Lumbar puncture; 30 c.c. of clear fluid removed under much increased pressure.

September 27. Lumbar puncture; 20 c.c. of clear fluid removed under normal pressure.

Upon leaving the hospital September 30 the child had flaccid paralysis of both legs, but the neck, vocal cords, back, chest, right arm, and left hand had cleared up.

This case shows clearly the type of advancing paralysis in a very severe case, with good result following the use of immune serum intraspinally and intravenously.

The severe toxic variety appeared with greater frequency than in other epidemics, some having comparatively little paralysis while others were paralyzed to a marked degree. In several instances a typical picture of acidosis was presented.

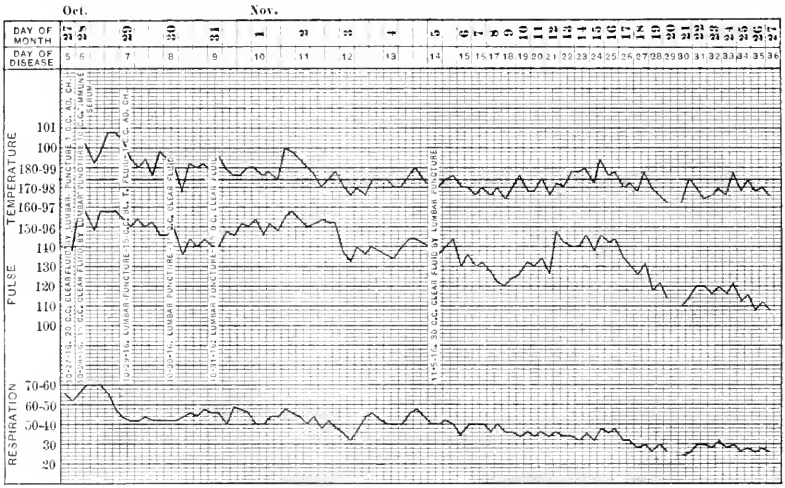


Chart of Case III.—S. H.

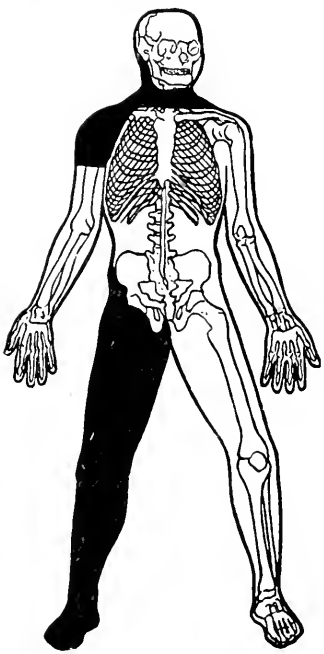
Case III.—*Progressive Paralysis with Toxemia.*

S. H.; male; aged eight months; breast-fed; mother accompanying child to hospital. History of fever and vomiting beginning October 23, 1916; onset of paralysis October 25. Upon admission to hospital October 27 the child showed marked toxemia associated with weak heart action; paralysis of neck; partial paralysis of muscles of deglutition; paralysis of vocal cords; intercostal muscles; respiratory movements, abdominal in character; paralysis of right shoulder and right leg; marked weakness in left leg. Knee-jerks on both sides absent; plantar reflexes present. Lumbar puncture gave 20 c.c. of clear fluid under increased pressure; 1 c.c. of adrenalin chloride was injected intraspinally.

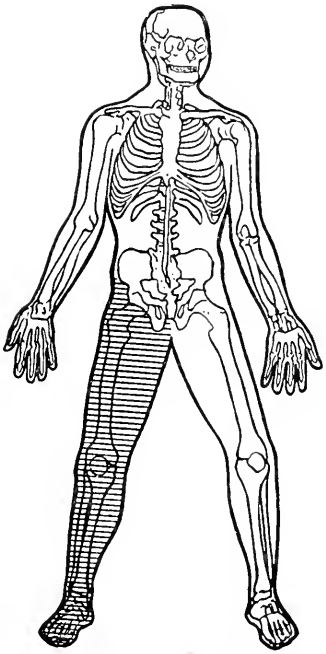
October 28. Lumbar puncture; 15 c.c. of clear fluid followed by blood-tinged fluid under moderately increased pressure. Cell count of the clear fluid 25 per cm.; 10 c.c. of immune serum injected intraspinally.

October 29. Heart action improved; general condition better; less toxic. Lumbar puncture; 15 c.c. of blood-tinged fluid under increased pressure; 1 c.c. of adrenalin chloride injected intraspinally.

October 30. Lumbar puncture; 15 c.c. of clear fluid under increased pressure.



CASE III.—S. H. On admission.



CASE III.—S. H. On discharge.

October 31. General condition much improved. Some chest expansion. Lumbar puncture; 15 c.c. of clear fluid under pressure; cell count 50 per cm.

November 11. Lumbar puncture; 30 c.c. of clear fluid under much increased pressure; cell count, 25 per cm.

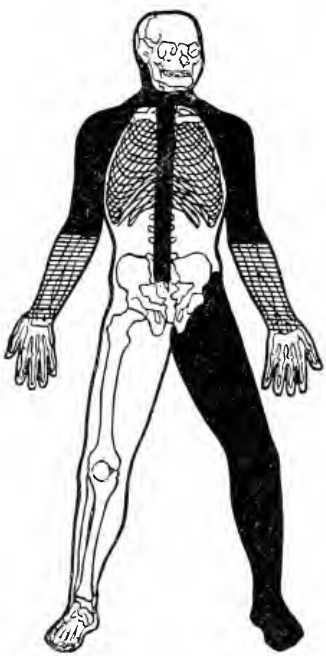
November 8. Movement of right shoulder normal; vocal cords and deglutition normal; movements of feet are stronger.

Upon discharge from the hospital, November 26, it was noted that all paralyses had cleared up with the exception of slight weakness in the right leg.

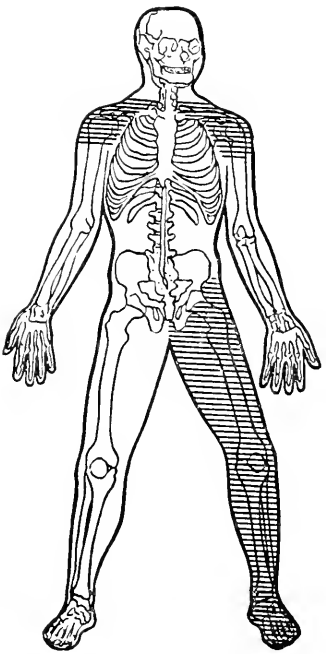
CASE IV.—*General Toxemia and Severe Paralysis.*

E. F.; male; aged nineteen years. Illness began October 14, 1916, with fever, constipation, vomiting, headache, followed the

next day by stiffness and pain in the muscles of the neck. Paralysis developed on October 17, the day of admission to the hospital. Examination showed stiffness of the neck and back; impaired chest expansion; flaccid paralysis of both shoulders and upper arms, with weakness of forearms; left leg completely paralyzed. Knee-jerk and plantar reflex absent on the left side, present on right. Toxemia marked; heart action poor. Lumbar puncture; 30 c.c. of clear fluid removed under increased pressure; cell count, 89 per cm.; 3 c.c. of adrenalin chloride injected intraspinally.



CASE IV.—E. F. On admission.



CASE IV.—E. F. On discharge.

October 18. Owing to toxemia, 10 c.c. hyperisotonic salt solution was injected intravenously at noon.

At 6 P.M. lumbar puncture; 30 c.c. of clear fluid removed; cell count 40 per cm.; 2 c.c. of adrenalin chloride injected intraspinally. Mildly delirious most of the time.

October 19. Noon. Eight cubic centimeters of blood removed and 10 c.c. of hyperisotonic salt solution given intravenously.

October 20. A.M. Lumbar puncture; 25 c.c. of clear fluid removed under pressure; cell count, 56 per cm.

At noon 10 c.c. of blood withdrawn and 10 c.c. hyperisotonic salt solution injected intravenously.

October 21. General condition continues the same; chest expansion not so good.

At noon 4 c.c. of blood withdrawn and 7 c.c. of hyperisotonic salt solution given intravenously.

October 22. Lumbar puncture; 22 c.c. of clear fluid removed under pressure; cell count, 53 per cm.

October 24. Lumbar puncture; 8 c.c. of blood-tinged fluid removed under pressure.

October 25. General condition much improved. Mind perfectly clear for the first time; chest expansion better.

October 26. On account of restlessness, lumbar puncture was done; 25 c.c. of clear fluid was removed under slight pressure; cell count 30 per cm.; 14 c.c. of immune serum injected intraspinally.

October 27. Chest expansion still improving; right shoulder, complete flaccid paralysis; right leg normal; left leg can flex but not extend or lift leg from bed. Kernig's sign present on both sides. Lumbar puncture; 30 c.c. of straw-colored fluid removed under pressure; cell count 100 per cm.

October 29. Lumbar puncture; 30 c.c. of clear fluid removed under pressure; cell count, 60 per cm.

Condition steadily improved until November 22, when he was decidedly irritable and complained of pain in the left elbow and shoulder, with inability to move it. Lumbar puncture was immediately done, removing 15 c.c. of clear fluid under increased pressure; cell count, 5. All symptoms cleared up within two to three hours.

When discharged from hospital, December 2, he showed normal condition of neck and back, almost complete chest expansion, normal motion of forearms and arms, slight weakness in both shoulders, left leg normal, motion in all directions but too weak to stand upon it. As this patient was in the hospital until the fifty-second day of the disease it was interesting to note the lessening of the paralysis and the marked regain in muscle power.

These two cases show clinically the toxemia which frequently occurs as part of the disease and also the severer type of paralysis, with recovery.

The most important complications were those pertaining to the gastro-intestinal tract, and here in bottle-fed babies difficulties quite frequently arose; while in the forty breast-fed babies which were treated in the hospital, the mother accompanying the child, there was practically no digestive disturbance and the death-rate was lower. Bronchitis was next in frequency as a complication, seen with greatest severity in cases with intercostal paralysis, bronchopneumonia occurring occasionally. Otitis media occurred as a complication in a small number of cases. It was rather remarkable that there were practically no complications due to nose and throat conditions. Repeated examinations of them revealed nothing abnormal. Diphtheria occurred in only three cases, but as the Schick test was always employed and antitoxin administered when

the reaction was positive, this will account for the small percentage of cases developing.

The diagnosis of this disease is of extreme importance, especially in the preparalytic stage, when, as a rule, it is most difficult. In this stage in cases presenting severe symptoms, such as high fever, rapid pulse, and respiration without any physical signs to account for them, a diagnosis of poliomyelitis can be safely made in most instances, but should always be confirmed by lumbar puncture and cell count of the spinal fluid, this being the only accurate diagnostic measure. Many cases, however, present pain and stiffness in the neck as well as muscle twitching, and here the diagnosis is readily made. The quantity of fluid obtained by lumbar puncture varies considerably, a small quantity being 10 c.c., while frequently 20 to 30 c.c., and in some cases as much as 50 c.c. is readily obtained. The fluid is crystal clear, and for the most part is under increased pressure, varying from rapid drops to a stream squirting out one or two feet from the patient. When possible the counting of the cells should be done at once, using the ordinary blood chamber and counting the leukocytes in ten squares, thus obtaining the number of cells per cm. It varies greatly in different cases, and at times in the same case when counted on different days. It is safe to say that a cell count over 15 and under 600 would make our diagnosis positive.

The treatment during the preparalytic stage is that of any acute illness plus isolation; a cathartic, rest in bed, fresh air, and care of diet. Lumbar puncture should be used not only for its diagnostic value but also as a therapeutic measure. It removes the excess of fluid from the spinal canal, thereby relieving pressure upon the cord. Adrenalin chloride has been used with apparent success at this time by injection into the spinal canal, following lumbar puncture, of from 1 to 2 c.c., depending upon the age of the child. Following its administration the buttocks should be kept elevated. If immune serum be available its use at this time would certainly seem more potentially effective. Since the great majority of our cases were not seen until paralysis had developed no definite conclusions can be reached regarding the value of serum during the preparalytic stage.

The care of the child during the acute paralytic stage is of even greater importance than in the preparalytic. Here, rest and quiet should be enforced, the child, however, not being allowed to remain too long in one position but moved from side to side and kept as comfortable as possible, as change in position lessens the probability of the development of pressure sores. Noise irritates and should therefore be avoided. Plenty of fresh air, but not too much direct sunlight, is essential. Hot baths, even during the early days, when moving the child to the bath-tub does not cause too much pain, improve the child's condition and at times relieve pain. Great care must be exercised in feeding, keeping up the nutrition to the point of tolerance without overfeeding, as digestion and assimilation are

in some cases greatly weakened. Pressure on the affected parts by bed-clothes is to be avoided by the use of cradles, and later light splints should be applied when early deformities appear.

While many drugs have been advocated and used there seems to be none which gives marked results. Hexamethylenamin was used in all cases during the first two and a half months of the epidemic without apparent result, and was then discontinued. Tincture of nucis vomicæ was used in many cases after the first week for its general tonic action without any bad effect, while in some cases the general condition of the patient improved. During the third and fourth week syrup of iodide of iron was used in a number of anemic children, with good result.

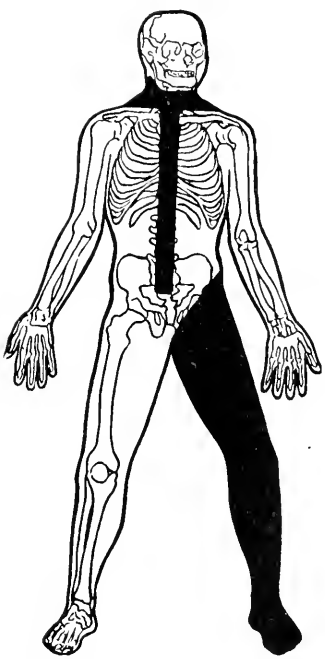
Lumbar puncture as a therapeutic measure must not be overlooked, as it is the one procedure from which is derived the greatest benefit. It should be done as often as the condition of the patient indicates; that is to say, from every twelve to every twenty-four hours in some cases; every three or four days in others, or only when increased pain and restlessness or irritability point to pressure by an increased amount of spinal fluid. By removing the pressure upon the congested portions of the cord we have seen cases recover from an apparent absolute paralysis of one or more extremities, which, of course, means there was only congestion and that the disease had not attacked or destroyed the nerve tracts. In other cases almost instant relief of pain followed lumbar puncture.

Adrenalin chloride in 1 to 1000 solution given intraspinally theoretically should be of great value because of its action upon the congested bloodvessels of the membranes and cord. Its use in doses of from 1 to 2 c.c. every six hours for several days has been advocated. This, however, we found caused marked disturbance, with vomiting in many cases, and every twelve to twenty-four hours was substituted. The results obtained were rather questionable, as it seemed impossible for the solution to reach the upper part of the cord if the seat of the lesion were high, even with the buttocks well elevated. This method of treatment, however, should not be given up until one showing decidedly better effect should be discovered.

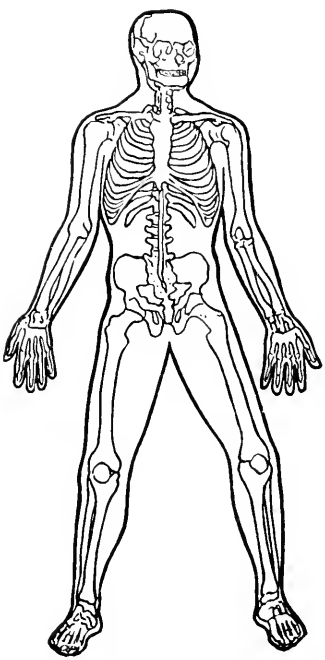
Normal human serum, that is, serum collected from healthy adults, was used in a few cases, but without result.

Immune serum, or that obtained from the blood of persons having suffered from acute poliomyelitis some months or years before, was used to as great an extent as possible. We were, however, handicapped by the comparatively small amount available, and by the fact that at first it was reserved for use in only the most desperate cases. Later on it was given to patients entering on the first or second day of the acute paralytic stage, and here some good resulted. It was given in doses ranging from 5 to 15 or even 30 c.c., either intraspinally, intravenously, or intramuscularly, daily or every two or three days for several doses. At times a combination of adrenalin

chloride in the morning and immune serum at night was used on consecutive days, with apparently better results than when given alone. In at least two very severe cases with chest involvement the improvement following this method of treatment was most marked. When, however, a severe toxemia is present, showing a marked general involvement, the intravenous use of the serum is especially indicated. When paralysis alone occurs the intraspinal method of administration seems to be most effective. The intramuscular method, I believe, should only be employed when it is impossible to give the serum into a vein, as the absorption is much slower. Another method of procedure when the toxemia is marked is the intravenous use of a hyperisotonic salt solution, following the removal of an equal or smaller quantity of blood; the quantity removed varying from 5 to 30 c.c., depending upon the age and condition of the patient.



CASE V.—L. K. On admission.



CASE V.—L. K. On discharge.

CASE V.—*Treatment with Adrenalin Chloride.*

L. K., Jr.; male; aged four years; admitted to hospital September 29, 1916, giving the following history (brother, aged two years, admitted same day): Began September 25 with fever, nausea, vomiting, headache, and convulsions. Paralysis developed on the day of admission. Examination showed neck and back rigid, left leg complete flaccid paralysis, knee-jerk absent, plantar reflex

present. Lumbar puncture gave 40 c.c. of clear fluid under much increased pressure; cell count 19 per cm.

September 30. Lumbar puncture; 5 c.c. of clear fluid under normal pressure; cell count 50 per cm.; 2 c.c. of adrenalin chloride injected intraspinally.

October 10. A.M. Lumbar puncture gave 12 c.c. of clear fluid; pressure moderate; cell count 30 per cm.; 2 c.c. of adrenalin chloride injected intraspinally.

P.M. Lumbar puncture gave 1 c.c. of clear fluid; normal pressure; 2 c.c. of adrenalin chloride injected intraspinally.

October 3. Good movement in toes and ankle-joint of left leg. Can flex but not extend it.

A.M. Lumbar puncture; 2 c.c. of clear fluid; pressure normal; 2 c.c. of adrenalin chloride injected intraspinally.

P.M. Lumbar puncture; 20 c.c. of clear fluid; pressure slightly increased; cell 30 per cm.; 2 c.c. of adrenalin chloride injected intraspinally.

October 4. P.M. Lumbar puncture gave 10 c.c. of clear fluid; pressure slightly increased; cell count 15 per cm.; 2 c.c. of adrenalin chloride injected intraspinally.

October 5. General condition good. Flexion but no extension of left leg; back and neck normal. Cannot bear weight on leg.

October 10. Can flex and extend left leg and also bear some weight when standing.

October 12. Can move left leg in all directions and stand with support.

October 15. Can bear weight of body on leg without support.

When discharged October 29, could stand and walk; simply slight weakness in left leg; knee-jerk still absent. Neck and back normal.

In this case the injections of adrenalin chloride were undoubtedly beneficial.

CASE VI.—*Severe Type of Paralysis Treated with Immune Serum.*

F. R.; female; aged three years; admitted to hospital, October 7, 1916, with the following history: Illness began October 4 with fever, constipation, and twitching of muscles of right arm. Paralysis noted October 6. Examination on admission showed flaccid paralysis of neck and back; right shoulder completely paralyzed; left shoulder and arm complete paralysis; right leg weak; left leg normal; knee-jerks absent in both; plantar reflex present. Lumbar puncture gave 20 c.c. of clear fluid under moderately increased pressure; cell count 23 per cm.; 2 c.c. of adrenalin chloride injected intraspinally.

October 8. Child became toxic. Lumbar puncture gave 5 c.c. of blood-tinged fluid under normal pressure.

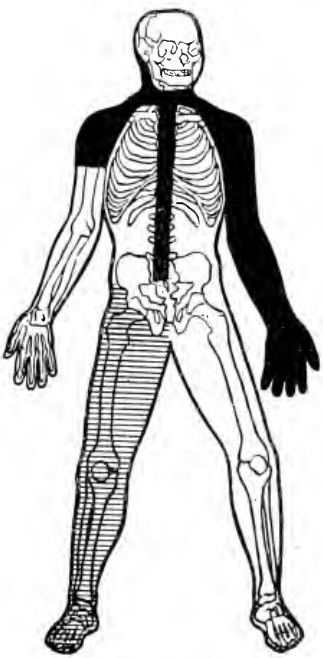
October 9. A.M. Three cubic centimeters of hyperisotonic salt solution injected into left external jugular vein.

P.M. Lumbar puncture gave 25 c.c. of clear fluid under increased pressure; cell count 20 per cm.; 15 c.c. of immune serum injected intraspinally.

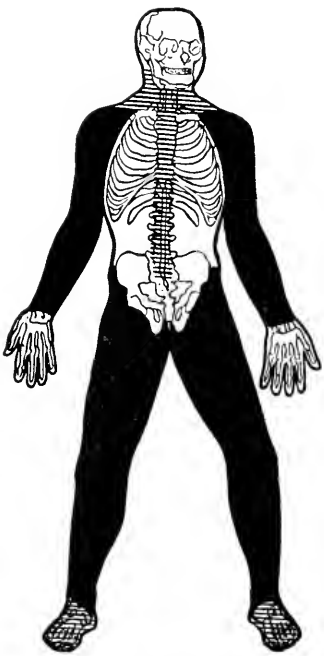
October 10. Chest expansion limited. Motion only in fingers; none in legs; Kernig's sign present.

October 13. General condition improved. Lumbar puncture gave 12 c.c. of clear fluid under greatly increased pressure; cell count, 40 per cm.

October 14. Complete flaccid paralysis of neck and arms, except for slight motion in fingers and legs.



CASE VI.—F. R. On admission.



CASE VI.—F. R. On discharge.

October 17. Motion in toes; chest expansion normal. Lumbar puncture gave 8 c.c. of clear fluid under normal pressure; cell count 16 per cm. Splints applied to legs.

October 19. Two cubic centimeters of hyperisotonic salt solution injected into the veins of the right foot.

October 20. Lumbar puncture gave 12 c.c. of blood-tinged fluid under much increased pressure.

October 21. General condition good. Slight motion in left leg.

October 27. Neck muscles stronger; right arm movements in fingers and forearm. Slight bronchitis developed.

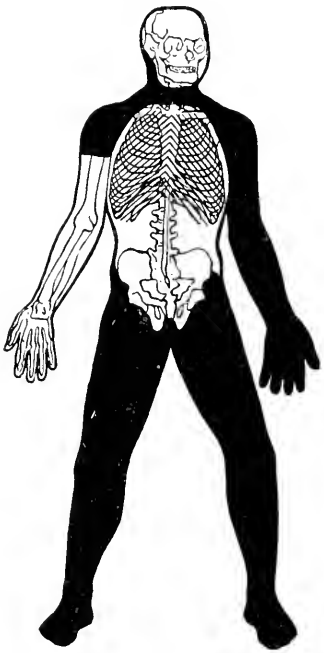
November 3. Bronchitis better. General condition good. Motion in both hands and wrists.

November 6. Lumbar punture gave 15 c.c. of blood-tinged fluid under moderately increased pressure.

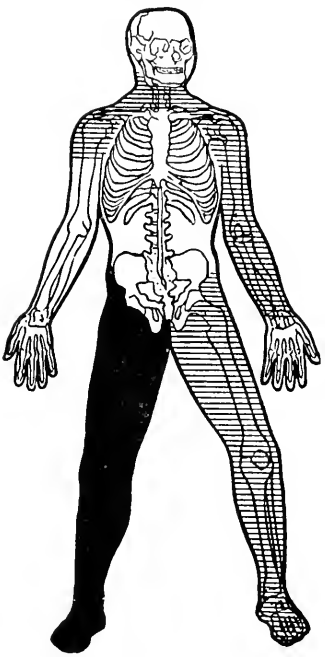
When discharged November 8, she had moderate control of neck and back. Shoulders and arms showed complete flaccid paralysis, motion only in hands; legs complete flaccid paralysis with motion in toes.

CASE VII.—*Severe Type of Paralysis Treated with Immune Serum.*

H. R.; female; aged two and one-half years; admitted to hospital September 20, 1916. History of fever, constipation, vomiting, and headache beginning September 16. Onset of paralysis September 18.



CASE VII.—H. R. On admission.



CASE VII.—H. R. On discharge.

Examination on admission showed paralysis of neck, chest, right shoulder, complete of left arm and of both legs. Knee-jerks absent; plantars present. Lumbar puncture gave 30 c.c. of clear fluid under increased pressure; cell count, 100 per cm.; 10 c.c. of immune serum injected intraspinally.

September 21. Right arm paralyzed; pain general. Condition very poor. Lumbar puncture gave 30 c.c. of clear fluid under pressure; 10 c.c. of immune serum injected intraspinally.

September 22. Lumbar puncture gave 8 c.c. of blood-tinged fluid; 5 c.c. of immune serum injected intraspinally.

September 23. Lumbar puncture; 10 c.c. of blood-tinged fluid removed under increased pressure.

September 24. Lumbar puncture; 15 c.c. of clear fluid removed under increased pressure; cell count 23 per cm.

September 26. Lumbar pucture gave 18 c.c. of clear fluid under slightly increased pressure; cell count, 33 per cm.; 7 c.c. of immune serum injected intraspinally.

September 29. Both forearms show limited movement. Slight vaginitis developed.

October 2. Lumbar puncture gave 8 c.c. of clear fluid under increased pressure; cell count, 24 per cm.

October 3. General condition much improved. Chest expansion much better on left side.

The general condition of the patient improved gradually, with better chest expansion, until she was discharged October 30, when she had fair movements in both arms, poor in shoulders; flaccid paralysis of right leg; slight motion of left leg; knee-jerk still absent; neck and back weak; chest muscles almost normal.

Case VI shows a severe type of paralysis, with toxemia improving to a certain extent by the use of immune serum. She undoubtedly would not have lived without its use, as she was in a desperate condition on admission.

Case VII was a still more severe type of paralysis when immune serum was used from the first, undoubtedly saving the child's life and at least assisting in the improvement of the paralyzed parts. Every child developing this type of paralysis before immune serum was used died, while it is safe to say that at least one-third lived where the serum was given.

Case VIII.—*Treatment: Combination of Adrenalin Chloride and Immune Serum.*

O. S.; male; aged six months; admitted to hospital October 1, 1916. History of fever and constipation beginning on September 25. Said to be recovering from bronchopneumonia. Onset of paralysis September 29. Examination on admission showed paralysis of neck; slight paralysis of chest; lungs normal with the exception of harsh breath sounds; left shoulder paralyzed; right leg complete flaccid paralysis; left leg very limited movement; knee-jerks and plantar reflexes absent on both sides. Lumbar puncture gave 25 c.c. of clear fluid under markedly increased pressure cell count, 26 per cm.; 10 c.c. of immune serum was injected intraspinally.

October 2. A.M. Lumbar puncture followed by 2 c.c. of adrenalin chloride injected intraspinally.

P.M. Lumbar puncture gave 40 c.c. of clear fluid under increased pressure; 10 c.c. of immune serum injected intraspinally.

October 3. General condition good; left arm paralyzed, excepting left hand; legs show slight movement of toes.

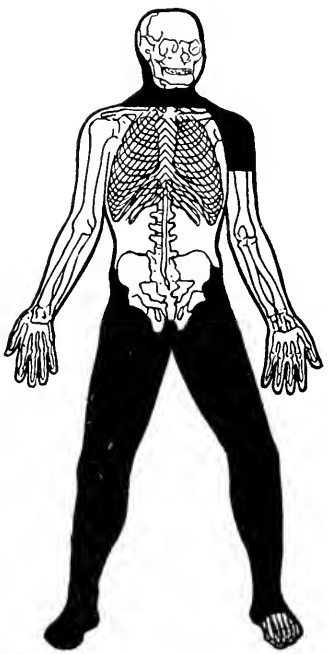
A.M. Lumbar puncture gave 25 c.c. of clear fluid; 2 c.c. of adrenalin chloride injected intraspinally.

P.M. Lumbar puncture removed 15 c.c. of turbid fluid; 15 c.c. of immune serum injected intraspinally.

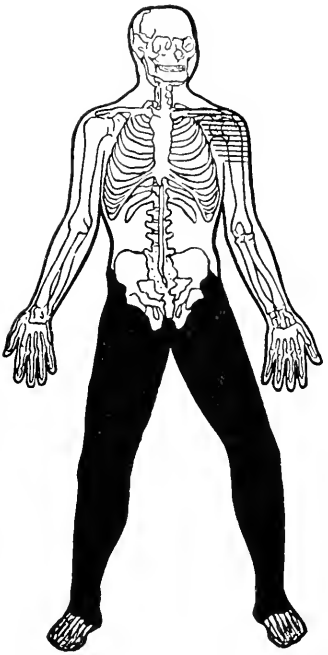
October 4. Left arm, good motion in forearm and fingers.

P.M. Lumbar puncture removed 10 c.c. of blood-tinged fluid under increased pressure; cell count 183 per cm.; 2 c.c. of adrenalin injected intraspinally.

Condition remained about the same until October 12, when a slight bronchitis developed. Movement of left forearm and fingers good. Right leg, complete flaccid paralysis; left leg, motion in toes.



CASE VIII.—O. S. On admission.



CASE VIII.—O. S. On discharge.

October 19. Bronchitis had cleared up. General condition good Neck only slightly weak; left arm showed slight motion in shoulder, good in forearm and fingers. Legs motion in toes only.

When discharged from the hospital November 2, neck was normal; left shoulder much stronger; could hold arm erect for a few moments; legs paralyzed except for slight motion of toes; chest expansion normal.

This child presented the most severe type of general paralysis, and without treatment would not have survived. The use of both immune serum and adrenalin chloride, we are convinced, were more efficacious than either one used alone. It is interesting to note that practically no severe reaction follows this method of treatment, with the possible exception when too large a dose of adrenalin

chloride is used. No marked changes in the temperature, pulse, or respiration were observed following the injections.

Since writing this paper an interesting epidemic in a private institution for feeble-minded children in a neighboring town has been brought to my notice. Thus far 5 cases have developed among the 12 inmates, with 1 death.

The first 3 cases were seen by me in consultation on December 9, 1916. The date of onset of the first case was November 21; the second November 28, and the third December 8. The fourth and fifth cases were seen December 15, having developed December 13 and 14 respectively. They are of interest from the fact that they are the only institutional cases to have developed during this epidemic in this section of the country, and further, that from the dates of onset it would appear that direct contact is clearly established as the source of infection, the only missing link being the source of infection in the first case.

Summarizing, it would appear to me that too little stress has been laid upon the abortive cases, many of which were never diagnosed, and it is to this cause that our high mortality rate of 29 per cent. can be attributed.

A further study of the gastro-intestinal lesions will, I feel sure, reveal the fact that this is one of the most important points of entrance for the infection.

Lumbar puncture, not alone for diagnosis but also as a therapeutic measure, must be borne more constantly in mind and used to an even greater extent. Adrenalin chloride and immune serum, either alone or in combination, is the most efficient treatment which has been evolved during this epidemic, and should be used whenever possible, only remembering, as in the case of diphtheria antitoxin, that the most beneficial results are obtained from its early use.

An interesting fact brought out in those cases detained in the hospital after the regular period of quarantine had expired, owing to pneumonia or vaginitis, has been the improvement in the parts which were apparently completely paralyzed on the date on which these cases ordinarily would have been discharged.

In concluding, while some advance has been made in the method of treatment during the recent epidemic, there is still a large field for research, and until the laboratory comes to our aid with a true antitoxin for acute poliomyelitis the clinician will be forced to admit that our mortality rate will remain higher than necessary.

EPIDEMIC VAGINITIS IN CHILDREN.[1]

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It has long been the opinion of clinicians that the clinical and bacteriological methods ordinarily used for the differentiation of gonococcus from other forms of epidemic vaginitis have not been sufficiently perfected to make them absolutely reliable. The literature of this subject, including the "Report of the American Pediatric Society on Vaginitis in Childhood," which was made to this Society in 1915, indicates that the bacteriological technic of this disease involved in the accurate diagnosis of gonococcus vaginitis, must still further be improved and simplified before it can be absolutely relied upon for the accurate diagnosis of epidemic vaginitis in institutional and private practice.

There is perhaps little doubt in the minds of pediatricians, as well as bacteriologists, that a large percentage of these cases are due to the gonococcus, and there is also no question but that the bacteriological tests as now made as aids in the diagnosis of gonococcus vaginitis are essential and are of the greatest value, and that at the present time we must rely almost wholly upon these tests in making our diagnosis of this condition, but the fact remains that the routine staining method for the Gram-negative, intracellular, biscuit-shaped diplococcus, which is chiefly relied upon in making the diagnosis of this disease, is not altogether satisfactory.

Prevalence of Epidemic Vaginitis in Children. Vaginitis is now recognized as one of the most prevalent infections in most of our large cities. This is especially true in hospitals and other institutions which care for female children. At the present time there are about seventy-five of these cases being cared for by the Cincinnati Hospital and the Children's Clinic, which is run in coöperation with this hospital. Under careful treatment and rigid quarantine regulations the number of these cases in the Cincinnati Hospital and Clinic have very materially diminished during the past winter. It is a significant fact that the vast majority of our new cases come from other institutions, such as orphan asylums and children's homes, and that nearly all of these new cases occur in children under school age. My inference, therefore, is that the public schools of Cincinnati have very little, if anything, to do with the spread of this contagion.

The marked prevalence of this disease in most of our large cities, as well as its intractability to treatment and its defiance of ordinary quarantine regulations, is recognized as presenting one of the most

[1] Read before the American Pediatric Society, May 9, 1916.

difficult public health problems presented by any of the contagious diseases.

The collective report of the committee above referred to indicates that the disease is on the increase. We may, therefore, assume that epidemic vaginitis is a contagious disease very prevalent among female children in our large cities, and that the means now in vogue for the cure of this disease and for preventing its spread are quite unsatisfactory.

During the long experience which I have had with this disease in Cincinnati there has never been an instance in which the disease was contracted by adults, although these cases are constantly under the care of female nurses. In the report of the committee above referred to, "85 physicians have never known of an instance in which a nurse was infected during a ward epidemic of vaginitis, 10 physicians have seen such an occurrence." It appears from these facts, therefore, that while the disease is very contagious in childhood, adults are practically immune. No satisfactory explanation has been offered as to the immunity of adults from this disease.

Means by Which the Contagion is Transmitted in Children. In children this disease is not in the ordinary sense a venereal disease, that is to say, the manner of its transmission is not by sexual contact. The contagion is carried to the vagina of the child in some way other than that in which gonorrhea is spread among adults.

The grouping of the various causes by which the disease may be spread among children is outlined in the report of the committee above referred to as well as in the voluminous literature of this subject.

The cases due to sexual contact are practically negligible. Here we have another marked difference between gonococcus vaginitis in children and in adults. It is a remarkable fact that a disease which in the adult is rarely transmitted in any other manner than by sexual contact should appear in children as a violent epidemic, spread in an altogether different way. The explanation of the difference in the manner by which this disease is spread in children and in adults has not received a satisfactory explanation. That the adult is very susceptible to the gonococcus contagion is a well-known fact; that children are equally susceptible to this contagion is fully recognized, and yet the manner in which the disease is spread in the child and in the adult could not be more unlike if in each instance it was an entirely different contagion. Is the explanation of these facts to be sought in some unrecognized change in the organism or organisms producing the disease, or in some peculiar change in the susceptibility of the vaginal mucous membrane to this contagion at different ages in the life of the individual?

Duration and Course of Epidemic Vaginitis Under Treatment. The report of the above committee as to the time required for a cure summarizes as follows: "53 of 71 physicians consider that the time varies from six weeks to six months. One believes that the cure comes only at puberty." That the absolute cure of this disease from a bacteriological stand-point is a matter of great difficulty in a very large percentage of the cases is the opinion of a large number of competent observers. That the disease very commonly, if relapses are taken into consideration, continues for years, even under careful medical supervision, is attested by the literature of this disease.

Every institution which pursues the careful follow-up system of its discharged cases finds that a large percentage of apparently cured cases are subject to relapse. My desire here is simply to call attention to the intractability of these cases under careful methods of treatment, and to the fact that many of them continue for years; yet notwithstanding the prevalence of this disease in childhood the disease practically disappears at puberty. There is no question in my mind but that there is a tendency to a spontaneous cure of this disease at this time of life.

In the report of the above committee only 11 out of 96 physicians were found who "had as adult patients those whom they had treated for vaginitis during childhood." When one considers the prevalence of this disease in young girls and its rarity in older girls, except when produced by sexual contact, one cannot but conclude that this disease in the vast majority of instances is self-limited. As a rule, it disappears as the child approaches puberty, under simple methods of home treatment such as ordinary cleanliness and mild soothing applications applied to the external genitalia. To my mind there is no other explanation for the disappearance of this disease at puberty, for surely the results of our present methods of treatment do not justify us in believing that the sudden disappearance of this disease at this period in the age of the child is due to systematic medical treatment.

Complications and Sequelæ in Epidemic Vaginitis in Children. My own experience as well as the literature of this disease leads me to believe that complications and sequelæ of epidemic vaginitis in children are much less common than gonococcus complications and sequelæ in the adult. Since 1905, when I encountered and reported an epidemic of this disease in the Cincinnati Hospital, I have had a very large experience with this disease, and during these years I have observed but one possible gonococcus complication (arthritis) in all of the cases that have come under my observation. In the report of the committee above referred to 39 per cent. of the physicians consulted "have seen more or less severe systemic complications," I believe, therefore, that complications and sequelæ in epidemic vaginitis in children

are vastly less common than are gonococcus complications in the gonorrhea of adults.

Methods of Treatment and Their Comparative Value. In the wide experience which I have had with this disease since 1905 when I reported an epidemic in the Cincinnati Hospital, I have had an opportunity to try many methods of treatment which have been suggested and I have been forced to the conclusion that the simpler methods of treatment such as irrigating the infected parts once a day with two quarts of a normal saline solution followed by the injection of 2 or 3 ounces of a 1 per cent. solution of nitrate of silver are more efficacious than the more severe forms of treatment involving the direct application of strong astringents and antiseptics to the vaginal vault and neck of the uterus. There can be no question as to the advisability of local treatment in these cases; such treatment undoubtedly shortens the course of the disease, and it is not improbable that one observer may get better results by reason of his superior technic with a certain line of treatment than other observers using the same treatment with perhaps less care and skill in the technic.

It is my belief that the intractability of these cases in hospital wards is largely due to reinfection. For this reason we have in the Cincinnati Hospital divided the vaginitis wards into four compartments. New cases are admitted into compartment one and there remain until the Gram-negative diplococcus can no longer be found in the smears taken from just within the vagina. They are then transferred to compartment two and are technically known as first negatives. There they remain under treatment for a week, and if the smear from the vagina at the end of that time is negative they are transferred to compartment three, where the treatment is continued, and are there known as second negatives. If at the end of a week a third negative smear is obtained they are transferred to compartment four and treatment is discontinued. Here they remain for a week or ten days, and if at the end of that time the smears from their vaginas are still negative, they are discharged to the institutions from which they came or into the care of the children's clinic which continues to look after them for a number of weeks to insure their convalescence.

Evils Which May Result from the Treatment of Epidemic Vaginitis. I have been much impressed with the idea that physicians have not given sufficient attention to the ill effects which may result from the long-continued local treatment of these cases. In the vaginitis wards of the Cincinnati Hospital my attention was recently called to the fact that a small percentage of the children in this ward were practising masturbation, and an inquiry developed the fact that three older girls of school age who had been in the ward for a long time were teaching the newcomers all kinds of bad habits. They were found to be imitating the physicians in making cul-

tures by introducing instruments into the vaginas of the younger girls. It was therefore felt that it was absolutely necessary to isolate these older children in order to prevent the development of these bad habits in the younger ones.

It is a self-evident fact that more or less harm may result from the frequent handling of the genital organs of these young girls, and this is especially true in cases in which the treatment must be continued over a long period of time. I here call attention to the ill effects which may result, especially from severe and frequent treatment not for the purpose of advocating the discontinuance of local treatment in these cases, but for the purpose of noting the fact that bad as well as good results may follow such treatment.

I have also found that very serious social problems have developed in the treatment of these cases in their homes. At the present time there are 45 of these cases in Cincinnati treated in their homes under the supervision of the Children's Clinic. These cases have been reported to the health authorities, and are therefore not permitted to attend school. They are, I believe, practically the only cases which are reported to the Health Department in Cincinnati. Most of these children are of school age, and many of them, by reason of the fact that they are excluded from the schools, are not only deprived of the educational advantages which the public school offers but they spend a large portion of their time in the streets under unfavorable hygienic and moral conditions. Many of these children go on for months with little or no vaginal discharge, and yet we may be unable for any length of time to obtain from them negative smears indicating that they are from a bacteriological stand-point cured of this disease.

I have been appealed to many times as to the injustice which is being done these children, and yet I have found no way of solving the problem. It is my belief that hundreds of these cases in every large city run a mild course and are unrecognized; these children go to school apparently without spreading the contagion; they have little or no treatment, and yet after a time they spontaneously recover.

It can be seen from the above outline which I have presented that the social and public health problems which this disease presents are very great, and that our knowledge of the disease, from the stand-point of diagnosis, quarantine, and treatment, are not sufficient to enable one to handle this question in a satisfactory manner.

In discussing the question of the handling of these cases by public health authorities, and whether or not epidemic vaginitis should be classed among the reportable diseases, let the physicians of this country ask themselves whether, in the present state of our knowledge of this disease, they would be willing to report to the health authorities a case occurring in their own families

the diagnosis of which rested solely upon the morphological and staining characteristics of the organisms found; that is to say, upon the fact that a Gram-negative, intracellular, biscuit-shaped diplococcus was found. If the term gonorrheal or gonococcus vaginitis were for the present dropped from the literature and the term epidemic vaginitis substituted (this name not suggesting to the lay mind a venereal disease), I think it would be much easier to handle these cases from a public health stand-point.

It appears to me very evident that until we are in a position to make vaginitis a reportable disease and enforce the ordinary health regulations which are used in other reportable diseases we are not justified in excluding these cases from our public schools.

HOW CLOSELY DO THE WASSERMANN REACTION AND THE PLACENTAL HISTOLOGY AGREE IN THE DIAGNOSIS OF SYPHILIS?

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The unimpeachable diagnosis of syphilis is made upon the demonstration of the Spirocheta pallida. After this fact became established the hope was entertained that the organism might be found regularly in syphilitic placentæ, but competent investigators declare that although prolonged search (Trinchesi[1]) is more frequently successful, the spirochetes are readily demonstrable in the placenta approximately in every third case of syphilis (Mohn,[2] Bab,[3] Graefenberg[4]). Generally, therefore, the diagnosis rests upon the less specific evidence of the histological changes in the chorionic villi or the Wassermann reaction in the mother's blood. As neither of these tests affords absolute proof regarding the presence of syphilis, we should know how frequently they point to the same conclusion; and, if not always, is one test more reliable than the other?

Besides variations in the Wassermann reaction due to the technic

[1] Bakteriologische und histologische Untersuchungen bei kongenitaler Lues, München. med. Wchnschr., 1910, lvii, 570.

[2] Die Veranderungen an Placenta, Nabelschnur, und Eihauten bei Syphilis und ihre Bezuhungen zur Spirochete pallida, Ztschr. f. Geburtsh. u. Gynäk., 1907, lix, 263.

[3] Bakteriologie und Biologie der kongenitalen Syphilis, Ztschr. f. Geburtsh. u. Gynäk., 1907, lx, 161.

[4] Der Einfluss der Syphilis auf die Nachkommenschaft, Arch. f. Gynäk., 1909, lxxxvii, 190.

employed[5] and to the interpretation of the degree of fixation, the specificity of the test is impaired, since occasionally a positive reaction is independent of syphilis. Thus, fixation has been observed in cases of malaria, of malignant growth, of hepatic disease, and of some tropical infections, as sleeping sickness. On the other hand, in an appreciable number of syphilities, the reaction is negative even during the secondary period of the disease. If interpreted in the light of the clinical history the reaction is rarely misleading, but this means, of course, that as yet implicit reliance upon the test is not justified. With newborn infants, Bar and Daunay[6] report notable inconsistency in the Wassermann; frequently they obtained a negative reaction when syphilis was known to exist.

It is also true that, one after another, the placental phenomena regarded as characteristic of syphilis have been questioned. Upon the gross appearance of the organ it is unsafe to base a diagnosis, for macroscopic signs of the disease are not constant; they were absent in 82 of 160 syphilitic placentæ which Mracek[7] examined. And, conversely, when the fetus dies sometime before it is born, whether syphilis is the cause or not, the placenta may be firmer than usual, its color may be a pale gray, and the maternal surface may have a greasy appearance.

Large placentæ do not, as was once supposed, necessarily denote syphilis. Labourdette[8] found that the relationship between the weight of the placenta and the weight of the fetus may not be used to establish a diagnosis. In cases in which syphilis was excluded, not infrequently this ratio was 1 : 5, 1 : 4, and occasionally 1 : 3. When the infant is premature this ratio is more significant, but prior to term we must remember that the placenta normally weighs more than a sixth of the weight of the fetus.

In the umbilical cord, as in the placenta, Emmons[9] had great difficulty in demonstrating spirochetes, and no syphilitic cord lesion is regularly found. An exudative inflammation about the vessels which Bondi[10] declared pathognomonic for syphilis may be caused by bacterial infection.[11] In typical cases when due to syphilis the infiltration appears at the fetal end; when due to placental bacteremia, at the maternal end of the cord. However, exceptions are frequent and greatly impair the diagnostic value of this lesion.

[5] Swift: Serum Diagnosis of Syphilis, Jour. Am. Med. Assn., 1916, lxvi, 599.

[6] Recherches sur le sero-diagnotic de la Syphilis chez la femme enceinte et l'enfant nouveau-ne (Methode de Wassermann), Obstetrique, 1909, n. s., ii, 192.

[7] Die Syphilis der Mutter und der Neugeborenen, Wien. klin. Wchnschr., 1903, xvi, 519.

[8] Gros Placentas et Syphilis, Paris Thesis, 1915.

[9] The Diagnostic Value of the Search for Spirocheta Pallida in the Umbilical Cord of the Newborn, Boston Med. and Surg. Jour., 1910, clxii, 640.

[10] Die Syphilitischen Veranderungen der Nabelschnur, Arch. f. Gynäk, 1903, lxix, 223.

[11] Slemons: Placental Bacteremia, Jour. Am. Med. Assn., 1915, lxv, 1265.

The most trustworthy evidences of placental syphilis to which Fraenkel[12] directed attention in 1873 are the histological changes in the chorionic villi. When freshly teased in dilute hydrochloric acid, originally recommended by Eckhardt,[13] or in water and examined under the microscope, the syphilitic villi appear abnormally large, opaque, and irregular in shape, with swollen ends. Characteristically the branching is limited and the bloodvessels are indistinct. While these findings are suspicious before the diagnosis of syphilis is made, stained sections should be examined. These provide a more satisfactory opportunity for studying the lesion.

The pathological process begins as a proliferative inflammation in the walls of the smallest bloodvessels—those of the terminal villi. Frequently the lumen of the vessel is obliterated. The enlargement of the villi is the result of the proliferation of the stroma. At last the syncytium which covers the villi proliferates and invades the underlying tissue.

While the changes in the villi constitute the most distinctive evidence of placental syphilis they have not been accepted by everyone as pathognomonic. In 1903 Hitschmann and Volk[14] observed a similar microscopic picture in cases in which a history of syphilis was unobtainable. "All the histological evidence thus far counted characteristic of placental syphilis," they dramatically conclude, "may be found in other conditions and even in normal cases. Perhaps these are cases of occult syphilis; who will bring the proof?" Since this question was asked the serological method of establishing the diagnosis has been devised; and we have accepted the opportunity to control the microscopic examination of the placenta with the Wassermann reaction in the mother's blood.

Two series of observations have been made, namely, the first upon 260 consecutive cases,[15] in San Francisco, in which the Wassermann reaction was made by Dr. L. S. Schmitt,[16] and the second upon 100 consecutive cases in New Haven, where Dr. A. L. O'Shansky[17] made the serological tests. These observations may be classified as follows:

Group.	Wassermann.	Placenta.	Number of cases.
I	Negative	Negative	243 (San Francisco) 93 (New Haven)
II	Positive	Positive	7 " " 3 " "
III	Negative	Positive	1 " " 0 " "
IV	Positive	Negative	10 " " 4 " "

[12] Ueber Placentarsyphilis, Arch. f. Gynäk., 1873, v, 1.

[13] Quoted by Rosinski: Die Syphilis in der Schwangerschaft, Stuttgart, 1903.

[14] Zur Frage der Placentarsyphilis, Wien. klin. Wchnschr., 1903, xvi, 822.

[15] Slemons: The Results of Routine Study of the Placenta, Am. Jour. Obst., 1916, lxxiv, 177.

[16] Both Doctor Schmitt and Doctor O'Shansky used two antigens, namely, (1) acetone insoluble alcoholic extract of ox heart, and (2) cholesterinized alcoholic extract of ox heart.

[17] Loc. cit.

In Groups I and II, which include 345 cases (95 per cent.), the Wassermann reaction and the placental histology agree absolutely and indicate the presence of syphilis in 10 cases, its absence in 235 cases.

The single case in Group III, in spite of the negative Wassermann, must be regarded as syphilitic. This woman, aged twenty-seven years, had four consecutive miscarriages. The pregnancy we observed ended spontaneously at the eighth lunar month. The fetus, 40 cm. long, weighed 1960 grams. The placenta weighed 480 grams (one-quarter the weight of the fetus) and the chorionic villi were definitely syphilitic. At autopsy upon the fetus the lesions of congenital syphilis were demonstrable. Therefore the weight of evidence points to the presence of syphilis, and we conclude that occasionally when the Wassermann reaction is negative the placental findings are more reliable.

Other investigators have found a negative Wassermann reaction in cases of syphilis. In the secondary period of the disease the test was positive in 87 per cent. of Bruch's[18] cases, 92 per cent. of Levaditi's, 96 per cent. of Blumenthal's, 98 per cent. of Blaschko's and 100 per cent. of Schmenfeld's. Later in the disease Kirschman[19] obtained a positive reaction in only 68 of 100 syphilitic patients. When the infant was syphilitic, Knopfelmacher and Lehndorff[20] failed to obtain a positive Wassermann in the mother's blood in 9 per cent. of his cases. If experience counts, these observations made several years ago are less accurate than serologists now obtain. At present many authorities hold that active syphilis is always accompanied by a positive Wassermann, though with latent syphilis they concede the frequency of a negative reaction approximates 20 per cent. (Kolmer[21]).

Group IV, comprising 14 cases (10 in San Francisco and 4 in New Haven), is not so discordant as would at first appear, for strong fixation (+ + +) occurred in only two instances. One of these patients was suffering from a streptococcus infection which probably was responsible for the positive reaction; at least the Wassermann test alone raised the question of syphilis. There was no history of a specific infection, and the chorionic villi were normal. On the other hand the fetal surface of the placenta was the seat of an inflammatory infiltration; streptococci were found in the subamniotic connective tissue and also in microscopic sections of the cord. On the third day of the puerperium the organism was isolated from the uterine cavity. The infant died of hemophilia; at autopsy none of the lesions of congenital syphilis were

[18] Bruch, Levaditi, Blumenthal, Blaschko, Schmenfeld, Kirschmann: Quoted by Labourdette (8).

[19] Loc. cit.

[20] Das Collesche Gesetz und die neuen Syphilis-forschungen, Jahrb. f. Kinderh., 1910, lxxi, 156.

[21] Syphilis and Life Insurance, Jour. Am. Med. Assn., 1916, lxvi, 1435.

demonstrable. Therefore the positive Wassermann would not seem attributable to syphilis.

Another case in this group with a strongly positive Wassermann reaction, but negative placental findings was syphilitic. On September 5 and again on the time of delivery, November 18, 1914, the serological test was positive. Furthermore, the mother gave a history of specific infection eight months previously and had not been treated. On account of the maceration of the fetus the autopsy findings were not helpful.

The teased chorionic villi were suspicious of syphilis, though the stained sections were negative. However, other areas of the placenta might have presented the characteristic evidence of syphilis, for normal areas may occur in syphilitic placentæ. Clearly in this case the weight of evidence favors the diagnosis of syphilis and indicates that occasionally the Wassermann reaction is more trustworthy than the placental histology—a situation which will exist most frequently in cases of postconceptional syphilis.

The remaining 12 cases of Group IV presented faintly a positive Wassermann reaction. The serologist reported 8 results as a single + (25 per cent. fixation) and 4 results as a double ++ (50 per cent. fixation). It is significant that 10 of these patients were suffering from eclampsia or a toxemia of pregnancy with albuminuria.

In the early history of the Wassermann test the occurrence of a suggestive or a positive reaction in cases of eclampsia was noted by Bunzel,[22] Daunay,[23] and others. Semon[24] obtained 3 positive, 9 negative, and 1 doubtful reaction in eclamptics without syphilis. We are unable to substantiate Semon's statement that the reaction is negative when the auto-intoxication is mild. On the contrary the severity of the intoxication bears no relation to the degree of fixation. A double + was twice reported when the albuminuria was of a mild type, while in several eclamptics with severe albuminuria we obtained a single +.

It is almost certain in these cases that the fixation was due to the metabolic disturbance. In similar circumstances Bunzel observed that the Wassermann became negative as the toxemic symptoms disappeared. We have not been able to make repeated observations upon our patients, but their histories excluded syphilis and the placentæ were normal. The infants were healthy at birth, in excellent condition when they left the hospital, and when visited four weeks later none of them had developed stigmata of congenital syphilis.

The frequency with which a positive Wassermann reaction

[22] Untersuchungen auf Komplementinde Substanzen im Blute von Schwangeren und Wochnerinnen, Zentralbl. f. Gynäk., 1909, xxx, 975.

[23] Quoted by Davis: Syphilis in its Relation to Obstetrics, Tr. Am. Gynec. Soc., 1916.

[24] Eklampsie und Wassermann Reaktion, Zentralbl. f. Gynäk., 1911, xxxv, 556.

occurs during toxemia of pregnancy and the question of its association with a definite form of auto-intoxication are pertinent problems. The limited data at hand will not permit an uncompromising view, but in our experience every third or fourth case of threatened and active eclampsia presents some degree of fixation, generally between 25 and 50 per cent. Whether syphilis underlies the toxemia is a question which can scarcely be raised, since Bunzel demonstrated that the serological reaction becomes negative as the auto-intoxication of pregnancy disappears.

In the course of chemical analysis of the blood having found that the cholesterol varies during pregnancy, and that the amount of this substance, while normal in some cases of toxemia, is greatly increased in others, we suspected that the latter group might be the one in which the faintly positive Wassermann reaction occurred. But this is not true. A negative Wassermann was reported for patients when the cholesterol amounted to 245, 180, and 125 mg. per 100 c.c., whereas 25 per cent. fixation was noted when the cholesterol was 144 mg.

In cases in which none of the classical symptoms of toxemia are present and the pregnancy apparently is normal, occasionally the Wassermann in the mother's blood is faintly positive. We encountered only two such cases, but Pedrini[25] observed the phenomenon more frequently, and in consequence records a positive Wassermann in 10.7 per cent. of the pregnant women he examined. Generally the reaction is faint, and without clinical evidence of syphilis it would be interpreted as negative. For the present the meaning of fixation in these circumstances is unknown, but probably it is explained by the presence of some substance in the blood referable to the metabolism of pregnancy. At all events the occurrence of the phenomenon in normal cases as well as toxemias emphasizes the value of controlling the diagnosis of syphilis with the microscopic study of the chorionic villi.

To recapitulate, the comparative study of the Wassermann reaction and the placental findings in 360 consecutive confinements indicates that the tests agree absolutely in 95 per cent. of obstetrical patients.

The chief source of confusion lies in the presence of a toxemia of pregnancy, which may be responsible for a faintly positive reaction. In these circumstances the fixation should not be taken to indicate syphilis, and accepting that interpretation, the serological test and the placentæ agree 99 times out of a 100.

Frankly contradictory results were encountered in three instances. One patient who gave a positive Wassermann was not syphilitic. The other two patients were syphilitic; the first presented a negative

[25] Una casistica di sieroreazioni di Wassermann nel campo ostetrico, Ann. di Ostet., 1910, ii, 365.

Wassermann but positive placenta, the second a positive Wassermann but negative placenta. Therefore it is impossible to say that one test is more reliable than the other, except in cases of postconceptional syphilis, and then the Wassermann reaction is more trustworthy. On the other hand, in latent syphilis the placental histology alone may confirm what is learned from the maternal history or the examination of the fetus.

At present the advisable procedure for the recognition of syphilis in parturient women begins with the study of the freshly teased chorionic villi—an examination which should be made routinely in obstetrical practice. If their appearance points toward the presence of syphilis, hardened and stained sections of the placenta must be studied and the Wassermann reaction in the mother's blood must be determined. Furthermore, all these observations should be made whenever the fetus is premature, macerated, or stillborn.

Instances in which the Wassermann reaction and the placental histology yield contradictory results are rare: If these cases are judged in the light of subsequent serological tests upon the mother, of facts in her history, and of the results of clinical or pathological examination of the fetus, they may be properly classified.

A STUDY OF VON JAKSCH'S ANEMIA.*

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Although cases of anemia accompanied by enlargement of the spleen and occurring in children were described clinically by Gretsel[1] as long ago as 1866, and pathologically by Cohnheim[2] in the preceding year, it was not until more than twenty years later, when the examination of the blood began to play a prominent part in clinical investigations, that the various conditions included under this head began to be separated one from the other. In 1889 von Jaksch[3] described a case of leukemia in a child, aged fourteen months, and in the following year[4] he reported 3 cases of enlarged spleen in children, a condition which he called anemia pseudoleukemica infantum. This was characterized by a diminution in the hemoglobin and in the number of red cells, marked persistent leukocytosis, sometimes glandular enlargement, slight enlargement of

* Read at a meeting of the Section on Medicine of the Academy of Medicine, January 18, 1916.

the liver, a marked enlargement of the spleen which was out of all proportion to the size of the liver, and a tendency to recovery. One patient died and the autopsy revealed no evidence of syphilis or leukemia. After this publication cases were recognized with comparative frequency, and there are numerous reports in the literature which deal with the subject. However, in spite of the comparatively abundant material and the obviously large amount of time which has been devoted to it, we have advanced but a very little way toward a clear understanding of the condition. Part of this is due, no doubt, to the lack of autopsy material, but the greater part is due to the fact that our investigations lead us to a blank wall, beyond which our present knowledge and methods do not permit us to penetrate. In this study of the condition, therefore, I shall have nothing very new or startling to present, but shall endeavor to clarify one or two points which have been the source of much discussion, and shall record the results of a method of treatment which, though not new, has not as yet been very extensively followed. Three cases of von Jaksch's anemia have rather recently been under observation in the New York Hospital, and form the basis for the present discussion.

Case I.—M. M., a girl, aged nine years, Italian, was admitted to the service of Dr. Conner on April 19, 1913. Her family history was negative. She had had measles in infancy, but gave no history that would permit one to suspect that she had suffered from rickets at any time. At the age of two years she is said to have had an attack of malaria, and since that time her spleen has been persistently large. Malarial organisms had never been demonstrated in her blood, but at the time of her first attack she was living in a district in which malaria was very prevalent, and for the next six years she is said to have suffered yearly with attacks of intermittent chills and fever.

The patient was well nourished and developed. Heart enlarged, apical impulse tapping, and a blowing systolic murmur was heard at the apex and transmitted but a short distance into the axilla. Over the aortic area this murmur was much rougher in quality. The liver dulness extended from the fourth rib to 8 cm. below the costal margin. The splenic dulness began in the axilla at the eighth rib, and the organ almost filled the left flank, extending to 14 cm. below the costal margin and almost to the median line at the level of the umbilicus. The spleen was hard and smooth and not tender. There were large, slightly tender glands under the angle of the jaw. Weight, 47 pounds. Eye-grounds and ears negative. Blood cultures and Wassermann negative. Von Pirquet test faintly positive. The stools were constantly positive for stercobilin and negative for bilirubin and blood. The urine showed a varying output of albumin, from none up to a heavy precipitate, with occasionally a few casts. Urobilin was constantly present. The

phenolsulphonephthalein output was 80 per cent. in two hours. The red cells numbered 2,300,000, hemoglobin 25 per cent., color index 0.5. White cells 8100,[5] polynuclears 58 per cent., lymphocytes 36 per cent., eosinophiles 1 per cent. The red cells exhibited marked poikilocytosis, anisocytosis, polychromatophilia, and basophilic granulation. There were 53 nucleated red cells for every 100 whites, 4300 per c.mm. A test of the resistance of the red cells showed that hemolysis began at 0.62 per cent. NaCl, and was complete at 0.44 per cent. "Vital staining cells" made up about 35 per cent. of the total number of red cells. Repeated attempts to find malarial parasites were unsuccessful. One examination of her blood serum showed no urobilin but a faint trace of bilirubin.

Her temperature varied between 100° and 102.° She was given arsenic until her tolerance limit was reached, and then was put upon quinin, a few doses intravenously, but most of it by mouth. Following the administration of the quinin her temperature fell during two days from 101° to 98°, but later rose again. During her second week in the hospital she developed a dry pleurisy which was relieved by strapping. Her red cells rose gradually to 3,900,000 and hemoglobin to 43 per cent., the index remaining at about 0.5. The nucleated red cells rose to 121 for every 100 white cells, fell to 3 and later rose again to 27, but were constantly present. Megaloblasts also were constantly found. The white cells varied somewhat, but rose to 13,500 before her discharge, which took place on June 16, 1913.

She spent the summer in the country and began at school in the fall. She then began to lose ground and to complain of pains in her legs and weakness. She was taken out of school, but gradually became worse, and for the two weeks before her second admission was unable to get about. She was readmitted to the hospital on January 12, 1914. At that time she showed marked pallor of the skin and mucous membranes. The heart signs were essentially the same as on the former admission. The liver dulness extended from the fifth rib to 10 cm. below the costal margin. The spleen had increased in size and now extended to within two fingers breadths of the symphysis and 2 cm. across the median line. The lymph nodes were not generally enlarged. Her red cells numbered 2,400,000, hemoglobin 25 per cent., color index 0.5. White cells were 15,000, polynuclears 40 per cent. The nucleated red cells were present constantly in small numbers. Her weight was 47 pounds. The urine showed only a faint trace of albumin and no casts. Her temperature varied between 100° and 103°. During the next two months she received arsenic most of the time. She showed no tendency toward improvement, and it was decided that the removal of the spleen might exert a favorable influence upon the course of the disease. She was, therefore, transferred to the first surgical division, and on March 21, 1914, Dr. Hitzrot removed a

spleen weighing 1420 grams and measuring, after fixation in formalin, 20 x 13 x 8 cm. It was surrounded by a number of adhesions, which made its removal rather difficult, and a hypodermoclysis was given during the operation. There were several small accessory spleens which were left in the abdomen.

Following the operation she had a rather stormy convalescence, with a sharp temperature reaction, though the wound healed promptly. On the day after the operation she had a marked normoblastic crisis, the nucleated red cells numbering more than 25 for each white cell. During the next six weeks she improved noticeably, the red cells rising to 4,100,000 and hemoglobin to 49 per cent., the index remaining at about 0.5. Her weight increased from 37 pounds immediately after the operation to 48 pounds on discharge. The white cells varied between 13,000 and 16,000. The nucleated red cells dropped in number rather rapidly, but rose again until, upon her discharge on May 5, 1914, they numbered five times as many as the white cells.

After leaving the hospital she continued to improve, and the following winter went to school and progressed satisfactorily in her work. When last seen on February 6, 1916, twenty-three months after the splenectomy, she seemed well in every way, and weighed 80 pounds. At that time the examination of her blood gave the following result: red cells 4,600,000, hemoglobin 65 per cent, color index 0.7. White cells 19,200, polynuclears 31 per cent. Nucleated red cells 138 for each 100 white cells, 2 of these being megaloblasts. The blood picture, as a whole, was essentially the same as upon her first admission to the hospital, except for the fact that the number of red cells and the hemoglobin percentage were both increased.

Case II.—S. K., a male child, aged eight months, was admitted to the service of Dr. William R. Williams on July 22, 1914. His family history was negative. He was a premature child, having been born at the seventh month of pregnancy. He was breast-fed for four months and then put upon a formula of modified milk. At the age of two months he had an attack of bronchopneumonia and two months later a second attack. At five months he suffered from gastro-enteritis. Since being put upon the milk formula, about four months before admission, he had failed to gain in weight, and in addition had suffered from restlessness, fretfulness at night, more or less sweating of the head, and constipation.

He was a poorly nourished, pale child, with no teeth, a square cranium, moderate rachitic rosary, and enlargement of the epiphyses at the wrists and ankles. The abdomen was prominent and the spleen enlarged, the edge being felt 6.5 cm. below the costal margin in the left nipple line. Weight 10 pounds 11 ounces. The Wassermann reaction was negative. The red cells numbered 1,400,000, hemoglobin 30 per cent., color index 1.0. The white cells were 37,000, polynuclears 33 per cent. There were 27 nucleated red

cells for each 100 white cells. During the next three weeks the condition of the patient remained the same, though the red cells rose to 2,300,000 and the hemoglobin to 45 per cent. The white cells varied from 17,000 to 54,000. Nucleated red cells were constantly present, at times rising to 61 per 100 whites. Megaloblasts were seen from time to time. On August 17, 1914, the patient was transferred to the second surgical division, where he was operated upon by Dr. Pool, who has reported the case.[6] After a transfusion, by which he received 150 c.c. of blood from his father, a splenectomy was performed, the organ weighing 105 grams and measuring 10 x 7 x 4 cm. Following the operation the child showed a definite clinical improvement, though his convalescence was impeded by the occurrence of rather frequent attacks of bronchitis. The red cells rose to 4,000,000 and hemoglobin to 85 per cent., the index remaining high. The nucleated red cells rose to 131 for every 100 white cells and the later fell. They were constantly present, though they fluctuated markedly in number. He was discharged on November 5, 1914, weighing only 12 pounds, but looking much better than he did on admission, and apparently improved. He continued his improvement for some little time until he developed another attack of bronchopneumonia, and died at home about two months after his discharge. No autopsy was obtained.

Case III.—A. A., a female child, aged eighteen months, was admitted to the service of Dr. William R. Williams on April 14, 1915. Her family history was negative. The patient was a full-term normal baby, was breast-fed for one year, and after that was fed both breast and bottle. She cut her first teeth at the age of twelve months. She had not talked or walked up to the time of admission. Her abdomen had been larger than normal since she was ten months old. Two months before admission she was sick for three weeks with an attack of pneumonia, since which time her abdomen has been more markedly distended. Appetite good. She had a slight cough for two weeks before admission.

The patient was a well-developed, fairly well-nourished child, weight 15 pounds 5 ounces. The central incisors only were present. The anterior fontanelle measured 3.5 cm. in diameter, the posterior fontanelle was closed. There was no craniotabes, but a rachitic rosary was present. The heart and lungs were negative. The abdomen was large and distended, the swelling being due in large part to the presence of an enlarged spleen, which extended to 15 cm. below the costal margin in the left nipple line. The edge was hard, firm, smooth, but not tender. The liver was felt 4 cm. below the costal margin. There were dilated venules over the surface of the abdomen. There were a few discrete enlarged nodes in the submaxillary, anterior and posterior cervical chains, and in the axillary and inguinal regions. The Wassermann reaction was

negative. The red cells numbered 2,700,000, hemoglobin 45 per cent., color index 0.8. White cells 12,000, polynuclears 47 per cent. There were 12 nucleated red cells for each 100 white cells. Myelocytes were rarely seen. There was marked poikilocytosis, anisocytosis, and polychromasia, and many of the red cells showed basophilic granulation. The urine was negative. The temperature ranged between 98° and 100°. Her condition remained unchanged for two weeks, when she was transferred to the second surgical division. On May 1, 1915, she was operated upon by Dr. Pool, who removed a spleen weighing 227 grams and measuring $14\frac{1}{2} \times 9\frac{1}{2} \times 3\frac{1}{2}$ cm. Following the operation there was acetone and diacetic acid in her urine for several days. She made a rather rapid convalescence, showing signs of improvement within a few days after the splenectomy. She then contracted measles, which was accompanied by a severe bronchitis, but which interrupted her convalescence only temporarily. Her red cells rose to 4,500,000 and hemoglobin to 60 per cent., and she was discharged on June 11, 1915, weighing 15 pounds 13 ounces, and very much improved. She continued her improvement, and was seen last on January 12, 1916, eight months after her operation, and twenty-six months old. At that time she looked very well. Her weight was 22 pounds; she had 12 teeth, and was able to stand, but did not talk or walk. Her red cells were 5,700,000, hemoglobin 67 per cent., and color index 0.6. Her white cells were 21,900, polynuclears 36 per cent., eosinophiles 6 per cent. She was said to have a good appetite and to eat everything, but it is probable that her diet is not nicely suited to her requirements. It has been very difficult to make the parents understand the necessity of feeding the child properly.

Von Jaksch's anemia may be defined as a condition occurring in children and marked by anemia, slight enlargement of the liver and marked enlargement of the spleen, and sometimes an enlargement of the superficial lymph nodes. The blood picture is characterized by a great diminution in the red cells and the hemoglobin and a persistent leukocytosis of varying degree. Nucleated red cells are nearly always present, sometimes in large numbers, and occasionally myelocytes are seen. Most of the patients show a definite tendency to recovery, though a few die. In those who live the abnormal blood picture may persist for a very long period of time even though the patient is clinically well. Anemia pseudoleukemica infantum, the name originally given to the condition, is not a very appropriate one, for the term pseudoleukemia has since acquired rather a special meaning, and the condition to which it is applied has no relation to the one under discussion. Of late years there has been a tendency to call it anemia splenica infantum, which is even less desirable, for splenic anemia is a descriptive term which is applied to a large number of unrelated conditions. Wentworth[7] and Sutherland and Burghard[8] have called attention to the necessity

of distinguishing von Jaksch's anemia from that form of splenic anemia without leukocytosis in children, a condition which seems to be entirely distinct from the one under discussion. Splenic anemia with leukocytosis occurring in children is a cumbersome phrase and it therefore seems preferable to retain the eponymic term and call it von Jaksch's anemia which has at least the merit of general usage.

Etiology. From the first it was noted that von Jaksch's anemia was frequently associated with rickets, and von Jaksch[4] was of the opinion that rickets played a certain part in its etiology. Nevertheless, he said it could occur in non-rachitic children, and several cases are reported in which no evidences of rickets could be found. In one of the cases here presented (Case I) there was no history or evidence of rickets, but there was a good history of repeated attacks of malaria, though the plasmodia were never demonstrated. Jungman[9] has reported a case in which a pregnant woman had a similar blood picture and recovered in two months after delivery. The baby also had the same condition, but became entirely normal in about three weeks. In some instances syphilis has been accepted as the causative factor,[10 11] while tuberculosis, gastro-intestinal upsets and infections, such as bronchopneumonia,[12] and malaria,[13] may all at times play a part. The view held by Grätz[14] that von Jaksch's anemia is merely an early stage of Banti's disease is apparently an unsupported belief. Although it cannot be said that rickets is the cause of von Jaksch's anemia, nevertheless there is apparently a certain relationship between the two.[15] They both occur at about the same time of life. The factors of importance in the etiology of the one appear also in the etiology of the other. Moreover, rickets is a disease in which the bone marrow is seriously affected and which is generally accompanied by more or less anemia, though the anemia and the obvious bone changes do not often parallel each other in severity. In addition, rickets is often accompanied by a leukocytosis, and in at least 20 per cent. of the cases there is more or less enlargement of the spleen. Marfan[16 17] even goes so far as to say that von Jaksch's anemia is rickets. His idea is that, in rickets, the primary lesion is a change in the bone marrow and a consequent compression of the osteogenetic portion of the bone, and that in those cases of von Jaksch's anemia in which there are no evident signs of rickets this disturbance of bone formation has not occurred. There is not sufficient evidence to support this belief. In early childhood the blood-forming centres are more or less unstable, so that they are apt to react intensely to a moderate stimulus,[18] and those factors which have been included as influencing the development of rickets and von Jaksch's anemia are the ones which are most apt to affect the hematopoietic organs. It is logical to conclude, therefore, from the available evidence, that von Jaksch's anemia is due to the action of toxic or infectious agents

which may or may not at the same time produce rickets. The source of these toxins is not necessarily in the gastro-intestinal tract.[19] The experiments of Courcoux and Ribadeau-Dumas showed that a guinea-pig injected with an alcoholic extract of fecal material from a patient suffering from von Jaksch's anemia might develop a similar blood picture,[20] but they were not sufficiently controlled, and the authors' deductions cannot be accepted. The relation between rickets and von Jaksch's anemia may be analogous to that existing between bothriocephalus infection and pernicious anemia. Either may exist alone, but the two do exist together in a notable percentage of cases, and it is impossible to escape the conclusion that they are in some way related.

Pathology. There is anemia of the organs generally, often associated with more or less fatty degeneration. There may be petechiæ, and in some instances there have been described hydropic collections in the body cavities. The chief interest, of course, centres in the hematopoietic organs, the liver, spleen, bone marrow, and lymph nodes. The lymph nodes are apt to be cherry red and enlarged, the so-called hemolymph nodes. The liver shows a reversion to the embryonal type of blood formation, and exhibits areas of hemopoiesis. The bone marrow is hyperplastic, of the myeloblastic type, and dark bluish red. Smears made from these organs reveal the presence of nucleated red cells.[18] The organ which has excited the greatest attention is the spleen. In this series of cases the spleens are of the greatest interest, since they show in a beautifully clear manner, three stages in the development of the pathological process. The earliest stage is seen in the spleen removed in Case III. The organ was bright red, the surface smooth and glistening, and the capsule thin. The consistence was rather tough and leathery. On section the cut surface was grayish red, with a sort of a brownish tinge, and very finely granular. The Malpighian bodies were numerous, about normal in size, and fairly well circumscribed. The trabeculæ were indistinct. On microscopic examination it is at once seen that the pulp is more cellular than normal, and that there are many minute hemorrhages in the splenic tissue, which is, however, not congested. The follicles present the appearance of having been compressed, being somewhat smaller than normal, with pale centre and dense periphery. There is a marked increase in the pulp cells, which are arranged in cords and strands. Scattered through the pulp are found small collections of large, rather pale-staining cells with basophilic cytoplasm. The nuclei contain definite nucleoli. They may be considered as undifferentiated mononuclear cells. Sections stained with the Jenner stain show many nucleated red cells and neutrophile and eosinophile myelocytes in the pulp. The mononuclear eosinophiles are strikingly numerous. Actively proliferating cells are seen in the sinuses.

The spleen from Case I presents an intermediate picture. The organ was of approximately normal shape, the capsule being everywhere smooth and transparent. On section the cut surface bulges considerably, is of a uniform dark brown color, smooth and shining, and rather firm and leathery to the touch. No trabeculæ or lymph follicles can be distinguished, the color being quite uniform throughout. Microscopic sections show the organ to be very vascular and considerably congested. There is also considerable diffuse connective-tissue increase which is most extensive along the trabeculæ. The follicles are small and rather poorly differentiated, the lymphatic tissue being greatly encroached upon by the spleen pulp. The sinuses still persist and are filled with the large undifferentiated mononuclear cells. These cells are distinctly more numerous than they are in the preceding section. The pulp is arranged in larger cords and strands than in the previous section, and when stained with the Jenner stain is seen to contain enormous numbers of neutrophile myelocytes and nucleated red cells. The same types of cells can be recognized as are described in the previous section.

In Case II the process has progressed still further. The spleen is normal in shape, fairly firm in consistence. The surface is smooth and bluish gray in color. The capsule is normal in thickness. The cut section is smooth, pale, and grayish red in color. The Malpighian bodies are few in number, extremely small, and indistinct. The trabeculæ are not prominent. The microscopic section shows at once a more extreme picture than is seen in either of the other two sections. The follicles are very small, the lymphatic elements evidently regressing. The pulp is more cellular, and is quite remarkably homogeneous in appearance, the undifferentiated mononuclear cells predominating and arranged in cords and strands so that they form a network through the whole pulp. There are also a number of so-called plasma cells which are still more basophilic in appearance. The sinuses are practically absent. The myeloidization of the spleen pulp is also evident in this section, there being many neutrophile and eosinophile myelocytes and nucleated red cells to be seen.

The picture then in the spleen is connective-tissue increase, atrophy of the Malpighian bodies and myeloid metaplasia. Ostrowsky's statement[13] that the atrophy of the follicles is due to connective-tissue increase was not borne out by the sections in our cases, it being apparently due rather to increase in the pulp element. The agreement between the histological pictures in the spleens from these three cases suggests that in spite of the differences in the clinical conditions presented, we are nevertheless dealing with a single pathological process. It is noteworthy that the most advanced stage was seen in the spleen removed from the youngest patient, the one who afterward died.

The symptoms of von Jaksch's anemia consist chiefly of the

symptoms of anemia in general, pallor, edema, weakness, dyspnea, etc., a large liver and very large spleen and a characteristic blood picture. Occasionally there is enlargement of the superficial lymph nodes, and there may be fever. The onset is gradual and the patient usually comes under observation with a well-marked enlargement of the spleen.[21] The symptoms which are due to the anemia itself may be masked by the presence of symptoms due to the accompanying conditions such as syphilis, tuberculosis, or rickets. The blood picture must be depended upon for a diagnosis. There is marked diminution in the hemoglobin and in the number of red cells. The color index is low in the majority of cases. Naegeli[18] says that the higher the index the worse the prognosis, and this is borne out by Case II of our series. Giffin's statement[22] that a high color index is characteristic of the condition is not borne out by the cases reported either here or in the literature. Nucleated red cells are generally present, often in overwhelming numbers, though some authors insist that their presence is not essential for a diagnosis. Megaloblasts are seen whenever the red cells are present in all marked numbers. One type of cell deserves special mention, since we believe it to be the parent cell of the megaloblast. The nucleus shows the radial structure, which is considered typical of the megaloblastic nucleus, while the cytoplasm is intensely polychromatophilic, having a peculiar slaty blue color. In many of these cells it is impossible to make out the presence of any hemoglobin, and they are probably often mistaken for lymphocytes. The nuclear structure is characteristic, however, and the existence of many intermediate forms renders it extremely probable that they are in fact the parent red cell. Certain it is that once recognized it is easy to pick them out in blood smears. In tissue sections it is more difficult, for the cytoplasm is not so clearly recognizable, and the nuclear structure is apt to be poorly defined. Such cells were found in the blood in all three of our cases. Their significance is quite the same as that of the megaloblast. There is apt to be poikilocytosis, anisocytosis and polychromasia, and a certain percentage of the cells show basophilic granules in their cytoplasm. These are all evidences of rapid blood regeneration. One of the most important criteria, as insisted upon by von Jaksch and supported by the later authors, is the leukocytosis. This varies greatly in degree even in the same case, and may be anything up to 50,000. The number of leukocytes may at times reach a comparatively low figure, as in our Case I, in which they were once as low as 8000. But a leukocytosis is not as significant in children as in adults.[23] The differential count shows for the most part a mononucleosis. The eosinophiles are about normal. This also is subject to great variations, and sometimes the polynuclears predominate. Myelocytes are not constantly present, but may generally be found. Myeloblasts,

plasma cells, and other abnormal white cells are occasional findings. It will be noted that this blood picture shows a great similarity to the one seen in pernicious anemia during a crisis, except for the color index, which is generally low in von Jaksch's. This has led Naegeli to conclude that the condition is most closely related pathologically to pernicious anemia.

Course and Prognosis. Von Jaksch described this condition as showing a tendency to recovery, and it is no doubt true that many of these cases do eventually recover. It must be admitted, however, that in some instances the condition has a fatal termination. One of von Jaksch's 3 cases died, as did 1 of ours, while Aschenheim and Benjamin[24 25] report 4 deaths out of 5 cases. Many of those who die do so from intercurrent infections, of which bronchopneumonia is the most prominent. The prognosis is, therefore, sufficiently serious. In those cases which do recover the return to normal is apt to be greatly delayed. The blood picture remains more or less abnormal long after the patient is clinically well. In those cases in which definite etiological factor, such as syphilis, can be shown, the prognosis is much better.

Treatment. The treatment has been unsatisfactory in the majority of cases. Since they frequently show a tendency to recover, almost any treatment may be followed by improvement. On the other hand, those cases which have progressed to a fatal issue have done so in spite of any treatment which has been given. In a few cases in which an etiological factor has been demonstrated, treatment directed toward that factor has resulted in cure. Labbe and Delille[11] report a rapid cure in an infant with cutaneous syphilides and a von Jaksch's anemia when treated with mercury. Iron, quinin, sunshine, fresh air, and change of climate have all been recommended. Stoos' cases[26] seemed to recover when given arsenic, while Stettner[27] had better results with thorium X. The most prominent feature of this symptom-complex is the enlarged spleen, and since to this organ has been credited the function of the destruction of the red cells, it was inevitable that, sooner or later, splenectomy would be resorted to as a therapeutic measure. Recently Giffin[22] was able to collect 4 cases of von Jaksch's anemia which had been treated by splenectomy. His report includes one of our cases previously recorded by Dr. Pool.[6] There is a possibility that McKendrick's case[28] was one of von Jaksch's though it is not very clear. The two additional cases mentioned here, therefore, make 6 in all which have been treated with splenectomy. The results are interesting, for in all of them the operation was followed by immediate clinical improvement. Wolff's case[29] was followed for three years, and though apparently well, still had a leukocyte count of 20,000. In Graff's case[30] the blood is reported as being "almost normal" nine months after the operation. Fowler's case[31] had been followed but five weeks, and in that time there was but little change

in the blood picture beyond an increase in the hemoglobin. In our Case I, although the child was apparently well eighteen months after her operation, the blood picture was essentially the same as upon her first admission to the hospital, some two and one-half years before. Case II died from bronchopneumonia before any lasting results could be seen. Case III eight months after operation still had a leukocytosis of over 20,000. It is evident then that the condition is not localized in the spleen, and that the other hematopoietic organs must be more or less extensively involved, in spite of Zamboni's statement[32] that the bone marrow rarely shows any changes. In all 3 of our cases the spleen was the site of active blood regeneration, and it is difficult to see how the patients could derive advantage from the removal of such an important centre for the formation of new blood cells. It may be said that the predominant activity of the spleen in these cases is a destructive one, and that the regenerative function is merely secondary, but we are without facts to support this hypothesis. Efforts to obtain hemolytic substances from the spleen in other forms of anemia have been unsuccessful.[33] Nevertheless we have the facts that the operation has been performed in six instances, and that in five of them it was followed by apparently lasting improvement. In this connection it may be interesting to refer to a case reported by Coupland[34] in 1896. He removed the spleen from a woman suffering from what was diagnosed as splenic anemia. Following the operation she showed a marked improvement. Two years later she died with symptoms of portal obstruction and an autopsy revealed extensive syphilitic involvement of the liver. It must be admitted that these cases would perhaps have recovered if left alone. But while under observation they showed no tendency in that direction, and there is no doubt that the splenectomy hastened their recovery. This form of treatment, therefore, has a large place in the therapeutics of von Jaksch's anemia, though it should not be adopted too hastily.

I wish to express my thanks to Drs. Conner, Williams, Pool, and Hitzrot for permission to report these cases and to Drs. Elser, Butterfield, and Tytler for material help in the preparation of this report.

NOTE.—Case I thirty-four months after the removal of the spleen is reported well. She was unable to come to the city for an examination of the blood at that time. Case III was seen on October 21, 1916, three years old and about eighteen months after her operation. She looked perfectly well, weighed $25\frac{1}{2}$ pounds, and had all of her first teeth. An examination of her blood showed 5,700,000 red cells, hemoglobin 89 per cent., index 0.78. The white cells numbered 15,700, polynuclears 24 per cent. No abnormal cells were seen. Since this paper was written we have had the opportunity, through the courtesy of Dr. Frederic H. Bartlett, of seeing sections of a spleen removed at the Babies' Hospital in the course of von Jaksch's anemia. The histological picture corresponded with that described in the cases reported in this paper.

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A CASE OF YEAST (MONILIA) INFECTION OF THE LUNG.

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Through the courtesy of Dr. A. C. Harrison, of Baltimore, I was recently enabled to study a case of yeast infection of the lung which is sufficiently interesting from various points of view as to warrant its publication.

Case History. The patient, J. E. S., male, aged about thirty years, an employee of a gas company, was sent to Dr. Harrison for examination, as his health had evidently been failing for about a year. While his normal weight was 148 pounds he now weighed only about 130 pounds. He complained of becoming tired very easily, had had occasional night sweats, and cough and expectoration. He would periodically feel quite normal, however, but his cough and expectoration would then return and again persist for a variable time. The patient's appetite had not suffered; there was no diarrhea and no history of ulceration of the skin.

With the idea in mind that he might possibly be suffering from tuberculosis, Dr. Harrison sent a specimen of the patient's sputum to me for examination. This was slightly mucopurulent and free from tubercle bacilli, but crowded with yeast cells occurring either singly or in budding form. This observation was so surprising that another specimen of sputum was secured under conditions which excluded every possible chance of accidental contamination. The finding in this was the same: there were no tubercle bacilli but innumerable yeast cells. The conclusion was accordingly that the patient was most likely suffering from an yeast infection of the lung.

As the physical examination revealed nothing abnormal, in particular no rales, no dulness, and no impairment of the breath sounds, a fluoroscopic examination was made by Dr. H. E. Ashbury, who reported as follows:

"The movements of the diaphragm are equal on both sides. There is some thickening of the bronchi leading to the upper lobes. Stereoscopic pictures show a diffuse infiltration about the hilum of both lungs, extending upward to both upper lobes and involving the right middle and lower lobes. The bases are only very slightly

involved. The appearance is that of tuberculosis, showing the interweaving of the bronchial markings with some studding of small calcified bodies, giving the appearance of mottling. Much of the thickening above the hila is due to glandular enlargement. The cardiovascular shadow is normal, and gives no evidence of involvement of the mediastinal glands."

The examination of the blood showed the following: Wassermann negative. Hemoglobin, 88. Red count, 4,664,000. Color index, 0.94. White count, 6500, of which 41 per cent. were small mononuclears, 5.3 per cent. large mononuclears, 51.3 per cent. polynuclear neutrophiles, 1.3 per cent. eosinophiles, and 1 per cent. basophiles.

The urine contained neither albumin, sugar, diacetic acid, nor acetone, and showed no increase of indican. Microscopically there was nothing unusual.

Examination of the feces revealed a few small oval, budding yeast cells, such as may be found in any specimen. Their cultivation (in a single attempt) was not accomplished.

Scrapings from the tongue showed no yeast cells. From the sputum the organism in question was readily obtained in pure culture, and has now been under observation for twelve months.

In the sputum the organism occurred in torular form only. The individual cells were nearly round, the majority occurred singly, and only occasional ones were budding. Their size was fairly uniform, averaging 6 μ. Viewed with the oil-immersion lense each cell showed a round highly refractive little body, measuring from 1 to 2 μ in diameter and smaller granules. Some of the cells appeared vacuolated, and with a certain focus their outline was doubly contoured. Unstained, the cells had a greenish shimmer. Treated with Lugol's solution the torular cells assumed a faint yellowish color. With the usual methods of staining no very satisfactory differentiation of the cell contents could be obtained, as it was difficult to avoid overstaining. With a very dilute solution of safranin, however, the nucleus could be brought out in most of the cells. Spores were not observed, nor were mycelial threads seen in the sputum.

In cultures, cells were occasionally seen which carried a daughter cell of almost equal size as the mother cell, from which in turn an elongated cell was given off, and from this a short row of smaller oval cells. At the same time cells were occasionally encountered which appeared sausage shaped, measuring 12 to 13 μ in length by 2.5 μ in breadth.

Cultures on agar grew out abundantly in twenty-four hours, and were of a white, creamy appearance and consistence. In these the organism still retained its torular form, with occasional premycelial types, the latter especially in cultures that had grown for a week or longer. But even after transplanting for twelve

months, at weekly intervals, the torular form predominates by far. Generally speaking the cells were for the most part smaller in the cultures than in the sputum, measuring from 3 to 6 μ in diameter, but much larger specimens were also quite common, and these usually oval, measuring 7 by 11 μ. In the cultures all the cells appeared provided with a large vacuole, which almost filled the body of the organism, and lying on top or within it a small highly refractive body.

In the young cultures most of the cells showed no buds at all: some were provided with a single bud, none with more. Several buds were only observed in old broth cultures.

On Petroff medium, containing gentian violet, a comparatively restricted growth occurred, in which numerous premycelial forms were noted.

In anaërobic stab cultures under oil, growth occurred along the line of the stab, and radiating out from this, as a central axis, large numbers of fine hair-like filaments penetrated the solid agar, so that at the expiration of about six weeks the appearance was that of a fine bushy tail in the substance of the agar. The growth first appeared while the tube was kept at incubator temperature, but later it developed at that of the room and showed a certain degree of heliotropism. Immediately under the oil a moderately dense mycelium developed with abundant lateral production of conidia. Frozen sections cut at right angles to the long axis of the cylinder of agar showed that the hair-like processes represent single mycelial threads with terminal as well as lateral bunches of conidia.

Chlamydospore-like terminal formations were occasionally encountered in the anaërobic cultures as well as on Petroff's medium.

True ascospore formation was not observed.

The hyphal threads of the mycelium were segmented.

A production of aërial hyphæ was not noted during the twelve months of observation. In plain bouillon the organism develops fairly readily, forming a granular-looking sediment while the supernatant fluid remains clear.

In liquid white of egg (alkaline) a similar growth is obtained, though it is somewhat less abundant.

Its behavior in litmus milk is especially striking. There is apparently no change during the first week or ten days, above all no acid production. After a longer period, however, there appears to be an increase in the alkalinity of the medium, while at the same time coagulation occurs; this state persists without subsequent digestion taking place.

Glucose bouillon is slightly fermented after twenty-four hours; in the next twenty-four hours this increases a little, but after that it seems to cease. Lactose, saccharose, inulin, and mannite are not fermented.

The organism is markedly pathogenic for rabbits. One animal

which had been given 5 c.c. of a bouillon culture intravenously at 11 A.M., January 17, was rendered quite ill, and was found dying early in the afternoon of January 20. At the autopsy, which was made immediately after killing the animal with chloroform, most extensive macroscopic lesions were found in both kidneys, which were studded with innumerable white nodules of pin-point size. These were confined to the cortex.

Equally striking was the appearance of the appendix. This was likewise studded with miliary nodules, which did not extend, however, macroscopically beyond the line of junction with the cecum. Microscopically, the lesions in question were essentially areas of necrosis, surrounded and partly infiltrated with leukocytes. Microscopically there was in addition the picture of an acute diffuse nephritis. In the appendicular and renal lesions the offending organism was found practically exclusively in mycelial form, while in the urine in addition to this the torular type was present in enormous numbers. In the lungs there were no lesions which were comparable to those in the kidneys and the appendix. Instead there were numerous hemorrhagic areas containing large numbers of the organism in torular form, but no evidence of mycelial production.

At the time of writing the organism has almost lost its tendency to produce mycelial forms even under anaërobic conditions, but is still pathogenic.

As regards the subsequent history of the patient I can add that following the administration of potassium iodide in full doses the cough and expectoration ceased, and that he has not only regained his former weight but has even added thereto. Apparently he is well, but whether *post hoc* or *propter hoc*, and whether or not the improvement will be lasting, it is of course impossible to say at present.

As regards the botanical position of our organism my feeling is that our present knowledge of the group of which it evidently is a member is as yet too meager to warrant any dogmatic statements. Its general biological characteristics are essentially the same as those of the organism which Bahr[1] and Ashford[2] regard as the cause of sprue, and which these writers view as monilia.

When I first discovered the organism in the sputum I was under the impression that the case was an instance of blastomycosis of the lung, but its smaller size, its disinclination to mycelial formation, its non-production of aërial hyphæ, and its marked pathogenic properties seemed to rule this out.[3] The absence of endosporulation and the very evident tendency to multiply by budding, on the other hand, distinguished it from the Coccidioides immitis of California.[4]

[1] Tr. Soc. Trop. Med. and Hyg., April, 1914, xi, No. 5.
[2] Am. Jour. Med. Sc., 1915, cl, 680.
[3] Stober: Arch. Int. Med., 1914, xiii, 509.
[4] Ibid., 1915, xv, 608.

The only other instance of monilia infection of the lung which has thus far been recorded is that of Boggs and Pincoff.[5] Their organism, it is true, gradually developed a tendency to mycelial formation, but its behavior in other respects is so similar to my own that I am inclined to regard the two as identical. Morphologically, theirs as well as my own are indistinguishable from that of Bahr and Ashford, but the evident affinity of the latter for the intestinal tract in the human being, and of Boggs and Pincoff's and my organism for the lung, would, for the present at least, warrant the separation of the two types, which might appropriately be termed monilia intestinalis and monilia pulmonalis respectively.

THE ROLE OF THE LEUKOCYTES IN VIRIDANS ENDOCARDITIS AND THE EFFECT OF NUCLEIN INJECTIONS.

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and

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The work of the past ten years tends to lay more importance on the vital activity of the white-blood cells and their enzymes than was accredited to them during the period of enthusiastic adoption of the humoral theories. While the hopes raised by the work of Petterson, Hiss, Zinsser and others that leukocytic injections would enhance resistance in various diseases have not been fulfilled, these investigations have served the purpose of bringing out the true value of intraphagocytic and extraphagocytic bacterial destruction and the balancing of enzyme and antienzyme. The behavior of leukocytes in frank pyogenic affections is fairly well understood, but in the more chronic diseases, and those with less activity of the leukocyte-producing tissue, the subject is far from clear. The value of the leukocytes as a defense in typhoid has only lately received any approximately acceptable estimation, and in tuberculosis we know practically nothing about it. In no condition would a thorough understanding of leukocytic defensive activity be more helpful than in subacute endocarditis, a pathogenic process whose inception and continuation imply a high degree of adaption of invaders to defenses. It was with the hope of learning something

[5] Johns Hopkins Hosp. Bull., 1915, xxvi, 407.

of these phenomena and of means to increase leukocytic value that these studies were undertaken.

Subacute endocarditis is a process consisting of a local pathological lesion in which bacteria are growing and multiplying, surrounded and protected by thrombosis and vegetative masses, and whence they occasionally escape into the blood stream. The organisms in the vegetation are somewhat resistant to the defensive powers in the blood, while those in the blood stream seem to have adapted themselves completely to both serum and leukocytes. They are relatively resistant to phagocytosis *in vitro* when freshly isolated, but the blood components having to do with phagocytosis are not necessarily reduced, and may, indeed, be actually above the values for normal sera. There is no bactericidal power of any value for the body's defense.

This being the case, immunity phenomena must be found, if present, on the part of the phagocytes. The facts of the matter, as shown by Rosenow, for endocarditis with pneumococci and related organisms, and our own work with Streptococcus viridans, are that opsonins may be subnormal or slightly increased, that phagocytic value in the patient's serum is low, and low or normal in normal serum. This lowered power of leukocytes in the presence of the patient's serum, Rosenow explains by the lack of a substance in the serum, distinct from opsonin, which stimulates intraleukocytic digestion, and probably another substance, possibly derived from the microbes themselves, which render cocci resistant to consumption and destruction. To confuse the worker in this matter, great variations occur in repeated examinations. In general, in our cases, the leukocytic or phagocytic average has been fairly low, the index low, and the patient's cells could be stimulated by normal serum. The suggestions of Rosenow are, therefore, acceptable in our 3 cases of viridans infection, but this is not so in a Streptococcus pyogenes case and one due to a diphtheroid.[1]

One very interesting viridans case gave the following test:

	Per cent. of phagocytic cells.		Phagocytic average.		
(*a*) Patient's serum + normal leukocytes	18	.5	.45	.83	.9
(*b*) Normal serum + normal leukocytes	12		.54		
(*c*) Patient's serum + patient's leukocytes	9	.75	.41	.95	.8
(*d*) Normal serum + patient's leukocytes	12		.43		

While this case shows indices falling within the range of error, it is, nevertheless, evident that the percentage of phagocytic cells is greater in the case of normal ones.

A second test gave practically the same figures, but a third one, two weeks later, resulted quite differently, and gains in importance in this study in view of the fact that the patient had had four doses of nuclein under the skin in the preceding week:

[1] Zentralbl. f. Bakt., lxx, 143.

	Per cent. of phagocytic cells.		Phagocytic average.		
(*a*) Patient's serum + normal leukocytes	26.5	.72	1.975	.88	.7
(*b*) Normal serum + normal leukocytes	25.5		2.25		
(*c*) Patient's serum + patient's leukocytes	19	.86	1.56	1.13	.6
(*d*) Normal serum + patient's leukocytes	22		1.38		

It will be seen by this chart that the serum index had not improved beyond the limits of error, yet the interaction of his own combination (*c*) and the reactive number of phagocytic cells had appreciably increased. In other words, then, while the serum values have not been seriously below the control, the former low value of the leukocytes, both in the patient's and normal sera, have been replaced by higher values and the former maladjustment of patient's serum and cells has been improved. (Compare *a* and *c* and *c* and *d* on both charts.)

The sum of evidence is, then, that the serum opsonin values may be nearly normal, but the phagocytic values are subject to great variations, usually appreciably below normal.

Complement-fixing antibodies have not been demonstrable in our cases, but in two viridans infections an anaphylatoxin could be found. The details of one case are worthy of citation:

(1) Cocci 0.5 c.c. emulsion, normal serum 0.5 c.c. G. P. complement 0.1 c.c. 37° C., 1 hour.
(2) Cocci 0.5 c.c. emulsion, pat. serum 0.5 c.c. G. P. complement 0.1 c.c. 37° C., 1 hour.
Pigs (all between 240 and 275 grams):
(A) 0.9 c.c., No. 1. No evidence of injection.
(B) 0.8 c.c., No. 1. No evidence of injection.
(C) 0.9 c.c., No. 2. Died in two minutes.
(D) 0.8 c.c., No. 2. Died in five minutes.

No. 3 began scratching almost at once; in a few seconds went into anaphylactic shock. Autopsy: marked emphysema, slight congestion, but no hemorrhage in gastric mucosa. Hemorrhage the size of a pea in pericardium.

No. 4 began twitching in one minute; shock appeared later than in No. 3 but typical. Autopsy same as No. 3, but no pericardial hemorrhage.

Subacute viridans endocarditis is, then, in all probability, a process due to a high pathogenicity locally, without bactericidal serum property, the circulating of bacteria and their anaphylatoxin and a lowered phagocytic power. The bactericidal effect is probably not missed, because antisera with this power are apparently of no value (Horder). Opsonins are powerless to stop the process because they can be raised by bacterin injections, with but little or no effect upon the disease. We are compelled, then, to investigate further the role of the phagocytes and the possibility of increasing their efficiency.

Phagocytosis is a process completed by the mutual relation of

chemotactically positive substances and cellular adequacy. It would appear from the work of Marchand, Bail, Rosenow, Gruber and Futaki and others that certain organisms in the process of active parasitism, whether due to virulence, capsule, aggressins, or what not, are distinctly difficult of consumption by phagocytes. Such seems only slightly true of Streptococcus viridans as normal serum and leukocytes, or even infected serum, will act upon them, there being, therefore, no antichemotactic power but probably antiopsonic power, which, as has already been cited, is accredited by Rosenow to some unisolated serum component. This may possibly be serum protease, for, as an anaphylatoxic state exists, this substance could be greater than normal (if one accept the theory of Jobling and his co-workers). At all events an anaphylactic condition is associated with leukopenia, and while we may not have a reduction of leukocytes in viridans infection, there is at least a very definite inadequacy of their phagocytosis and possibly of their number. Possibly they are kept busy supplying some neutralizing body for the antiopsonic power of the bacteria. It was recognized by Friedberger that in diseases like typhoid, where anaphylaxis can be shown, there is a lowered chemotaxis and a low leukocyte count; such conditions are said to respond to bacterial injection by a rapid and pronounced leukocytosis (Gay and Claypool). Unfortunately this does not occur satisfactorily in viridans infection, and we shall have to use other than bacterins for leukocytic stimulation.

Leukocytes respond to the liberation of protein of any kind, but especially of nucleoprotein; in other words, nucleoprotein has a pronounced chemotactic power. This is well shown in the leukocyte accumulations around bacterial bodies, dead or alive, or when the cells themselves have undergone destruction. This property has been thought of many times and use made of it in injecting nucleins to produce leukocytosis. The clinical use of this substance has fallen into disrepute for several reasons, the best probably being that it has not been thoroughly studied. We have repeated many of the old experiments with the hope of learning more of its properties and to see if it can be of value in viridans infections. The old controversy as to the value of increased leukocytes alone and their content of antibodies, while far from a complete settlement, does not affect the case.

In reviewing the literature germane to this subject we find no experimental or clinical work on the use of nuclein in viridans endocarditis, nor indeed, except bacterins, of anything which is supposed to act upon the leukocytes. The literature on nuclein in its theoretical value and practical therapeutic use, is relatively limited, most of the articles dating from the period in which there was an active controversy about the source of the bactericidal power of the blood. Vaughan, Buchner, and Hahn believe that

they increased the resistance of experimental animals to the introduction of various germs when nuclein was administered either before or after the organisms. Vaughan, having isolated the constituent of normal serum to which he ascribed natural protection, and finding it undigested by pepsin, believed it to be nuclein. Then there followed the dispute as to the origin of antibody and complement, a matter now on a working basis, although not settled. Whether or not leukocytes produced either or both, the results of the work of Petterson, Hiss, Mainwaring and others indicate clearly that some bactericidal power is to be found in the white blood cells and their extract, substances rich in nuclein. The act of phagocytosis is not sufficient to destroy parasitic organisms, and, as is shown by Neufeld and Rosenow, phagocytosis and intracellular destruction do not go hand in hand. Phagocytosis is due to appropriate chemotactic relations, while digestion is due to intracellular enzymes. The failure to complete both functions in every case is not understood. A persistent high number of leukocytes is indicative of a high resistance to organisms which have the chemotactic activity to call forth the cells; but it would seem that in subacute infections there is, despite the fairly high leukocyte count, an inadequacy on the part of the digestive intracellular power. Whether or not a great increase in white cells will supply this power, and whether or not nuclein could be the inciting agent for this purpose, are facts to be settled. The power of nuclein to produce an increase of leukocytes has long been known, and is ascribed in its therapeutic use to Horbaczewsky, a name mentioned by two writers, but we fail to find the original article.

The information about nuclein in the literature may be considered from three stand-points: how nuclein acts, the number and character of the leukocytes in the blood after injection, and the therapeutic effects. The opinion held by most observers is that nuclein exerts a distinct chemotactic effect on the leukocytogenic organs with the appearance of new cells. Others, notably Mendel, consider the new cells as appearing in response to destruction of old ones, this being due to the nuclein introduced. Still others believe there is a squeezing out of leukocytes from tissue spaces by contraction of involuntary muscles, which follows a subsidence of internal vasodilatation, a condition of the vessels shown by Mendel. There is less divergence in the observations upon the kind and number of circulating white cells. Nearly all authors find a decrease in total cells, followed by an increase, and most of them note an increase of the small lymphocytes and decline of the polymorphonuclear neutrophiles. We shall show that this is only a percentage increase and decrease. It is historically interesting to mention that Ames and Huntly cite a primary increase in the lymphocytes as a high percentage of young forms, whereas later the adult or polynuclears are increased. Pankow expressed little faith in

nuclein, believing the effect to be due to saline solution; this we shall see is erroneous. The experimental and clinical therapeutics of nuclein begin as far back as 1892 by Löwitt, then by Vaughan in 1896, after which no one seems to have worked much with the substance until the period 1903 and 1907, during which time several articles appeared. The most noteworthy of these are three coming from the Mikulicz Clinic by Mikulicz, Miyake, and Renner. They found that by the use of yeast nuclein they could increase the resistance of experimental animals to artificial infection and could materially reduce the morbidity and mortality from postoperative peritonitis. They lay stress on the fact that they could get greater protection and greater number of leukocytes (20 to 8) by the use of nuclein than by the use of aleuronat, which they class as a mechanical attractor of leukocytes. Renner, experimenting with dosage in human beings, used 50 c.c. of a 2 per cent. solution, which means 17 mg. per kilo for a man of 70 kilo. There was usually a mild general reaction and a local puffy, sensitive swelling at the site of inoculation. Their own description of the after effects is not in harmony with their nonchalance as to the severity of the reaction. Judging by the reaction we observed in dogs, this injection must be painful. According to Renner, the reaction on the part of the leukocytes takes place anywhere from six to twenty-four hours later, and one cannot foretell when it will appear or when the effect or the decrease will be greatest. The leukocyte increase is usually pronounced, being in his highest case 452 per cent. They say that this procedure, while of distinct clinical value, is not effective against fulminating streptococcal infections.

THE INTERPRETATION OF CERTAIN BLOOD-PRESSURE RATIOS.

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During the past ten years blood-pressure determinations have apparently become an essential part of the data necessary in many instances to an understanding of conditions affecting the circulatory system. In this period much of value has been acquired from blood-pressure studies. It will be the purpose of this article to interpret certain phases of the subject, although it is realized that in the words of a contemporary, "It is not difficult for the majority of us to be beyond our depth before we know it, when we venture in these waters."[1]

[1] McCrae, T.: Am. Jour. Med. Sc., April, 1916, in review of Sir Clifford Allbutt's Diseases of the Arteries, Including Angina Pectoris.

Types of Arteriosclerosis and their Influence upon Hypertension. From the beginning of blood-pressure determinations it has been apparent that not all types of rigid arteries were associated with hypertension. In fact, it is a matter of common observation that extreme sclerosis may exist with normal or decreased pressures. A review of the various types of arteriosclerosis may therefore be of interest at this point in an endeavor to correlate subsequently in this article various types of vascular disease with arterial pressure variations, and their clinical manifestations.

The Nodose Type of Arteriosclerosis. This is the most common form, and is characterized by whitish, flattened, and nodal thickenings of the intima. These thickenings or nodes are especially noticeable at points where smaller branches are given off from the larger arteries, such as the intercostal branches of the aorta. The aorta is, however, usually involved throughout the entire length. These nodes are the result of true hyperplasia of the connective-tissue cells of the intima, and are not the result of round-cell inflammatory infiltration. The nodes are non-vascular and may subsequently undergo localized necrosis, the so-called atheromatous ulcers, the areas of which are replaced by granulation tissue with eventual calcification and atheroma. The characteristic change is calcification and atheroma of localized patches or nodes of intimal connective-tissue overgrowth.[2] [3]

This type of arterial degeneration is not, as a rule, associated with hypertension, since the localized patches when present do not cause material contraction of the lumen of the smaller vessels.

The Senile Type of Arteriosclerosis. This type, the so-called "Moenckeberg's Sclerosis," is characterized by muscle atrophy and degeneration of the media. The muscle atrophy of the media is more important than atrophy of the elastic tissue. Compensatory overgrowth, or hypertrophy of the intima, may occur with subsequent atheroma of these areas of intimal overgrowth, or, as more frequently happens, sacculation and dilatation of the larger vessels, such as the aorta occurs, due to localized giving way of the intima. Calcification and fibrosis of the media is the essential change. This may involve the smaller vessels also, which are rigid. Savill[4] has shown in a report of 400 autopsies on individuals of an age of sixty years or over that an extensive patchy atheroma was consistent with an average longevity and absence of cardiovascular symptoms. Of course, if the patches of intimal overgrowth happen to involve the orifices of the coronary arteries the nutrition of the myocardium will suffer and will be followed by cardiac symptoms,

[2] Adami, J. G.: The Nature of the Arteriosclerotic Process, Am. Jour. Med. Sc., October, 1909.

[3] Adami and McCrae: A Text-book of Pathology, 1914, p. 487.

[4] Lancet, London, 1904, p. 506.

the variety of which will depend upon the degree of obstruction. If conditions producing "hypertonus" as described by Russell[5] have been present during the time the fibrosis of the media was progressing, it is conceivable that contraction of the peripheral vessels would occur with exaltation of arterial tension. As a rule, however, the senile type of arteriosclerosis is not accompanied by marked hypertension, for while the peripheral vessels are generally rigid they are not contracted, and hypertonus appears to be lacking.

Toxic Type of Arteriosclerosis. In this type the plaque-like nodes or patches of the intima have a translucent appearance and may resemble the nodose type, but the essential change is an inflammatory degeneration of the media. The initial nodes are more spread out and occur characteristically in groups especially in the ascending aorta and arch. These nodes are the result of a compensatory hypertrophy, but there is little tendency to calcareous change and atheroma, as in the nodose type. The toxic type of arteriosclerosis is essentially inflammatory and is seen particularly as a result of the toxins of syphilis, diphtheria, diabetes, and after lead and mercurial poisoning. The toxin of syphilis leads especially to intimal overgrowth, the nodes having a puckered appearance, with their long axis transverse to the long diameter of the vessel. In syphilis the vasavasorum of the first portion of the aorta are particularly affected, and round-cell infiltration occurs about their branches in the adventitia and media. The toxins of typhoid fever seem frequently to have an ill effect upon the intima of the peripheral arteries, the manifestations of which are to be seen in patches of overgrowth. The diphtheria toxin particularly affects the media.

In chronic degenerative diseases affecting the permeability and function of the kidneys the characteristic arterial changes of the toxic type are seen. In addition, hypertonus seems to go hand-in-hand with so-called chronic glomerulonephritis. It has been generally believed that the degenerative media changes in the arteries are brought about by the increased pressure resulting from disturbed kidney function and that ultimately contraction of the arterioles occurs.

Leonard Hill has shown that increased pressure in the larger trunks normally causes the arterioles to contract, and that the higher the pressure the more the arterioles tend to contract. It is this tendency to contraction of the lumen of the arterioles in this type of arterial degeneration which distinguishes it from the types before mentioned. The diastolic pressure is in consequence higher in this group. Allbutt[6] apparently believes in the hypertonus factor described by Russell, for he has protested against the use of the term arteriosclerosis as a disease *per se*. He believes that the arterial degenerative changes may occur as a result of any cause producing

[5] Arterial Hypertonus, Sclerosis and Blood-pressure, Edinburgh, 1907.
[6] Brit. Med. Jour., October 20, 1906.

high pressures. Savill[7] and Russell[8] have been able to demonstrate an increase in the muscular coat of the smaller arteries accompanying arterial degeneration in the larger trunks. This hypertrophy, they believe, implies abnormal contraction. This is in accord with the belief of Hasebroek[9] that contraction of the arteries is an active muscular act to assist the heart in maintaining an adequate pressure for blood flow, while dilatation of the arteries is a passive result of the injected volume of blood during systole. Adami and McCrae[10] have expressed their belief as to the relationship between hypertonus and arteriosclerosis as follows: "We support the view that arteriosclerosis as such is not in general of infective origin, and indeed is not an inflammatory process. We hold that it is the expression of a disordered relationship between the internal pressure to which the artery is subjected and the strength of the arterial wall, that strength depending in the main upon the condition of the media."

The Auscultatory Method of Pressure Determinations. Both systolic and diastolic pressures are best taken by auscultation, with a stethoscope of the disk type, over the brachial artery on the inner aspect of the arm below the compressing arm band. Korotkoff[11] first described this method in 1905. In applying this method, compression is made in the arm band to a point above which all sound is heard in the artery. The air-pressure is then gently released, and as the pressure falls the point at which the first sound is heard is taken as the systolic pressure. A series of similar clear sounds are then heard which are soon replaced by a series of murmurs, and a second series of clear sounds. These clear tones are shortly replaced by dull tones which rapidly disappear. Korotkoff believed that the diastolic pressure corresponded to the first dull tone following the second series of clear sounds. This is, as a rule, about 5 mm. above the point of disappearance of all sound.

Latterly, Hooker and Southworth,[12] using the Erlanger instrument in combination with the method of Einthoven and Geluk for recording brachial sounds, have expressed the opinion that for clinical purposes the point of cessation of sounds in the artery corresponds with the diastolic pressure. I have taken the dull tone following the second series of clear sounds as indicative of the diastolic pressure, but am inclined to believe, with further experience, that in the majority of cases of rapid heart action this transition is exceedingly difficult to determine. It would undoubtedly simplify the procedure if the point of disappearance of pulse sound was taken as the diastolic pressure. Further experience will probably show the wisdom of adopting this point, since for all practical accuracy it answers the purpose.

[7] Tr. Path. Soc. of London, vol. lv.
[8] Loc. cit.
[9] Deutsch. Arch. f. klin. Med., 1911, cii, 567.
[10] Loc. cit.
[11] Mitt. d. k. mil. med. Akad. zu St. Petersburg, 1905, xi, 365.
[12] Arch. Int. Med., 1914, xiii, 384.

The Systolic Pressure. For nearly a decade after the estimation of blood-pressure became a matter of clinical interest, attention was largely directed to the systolic pressure. The literature to about 1910 in fact mentioned but rarely any other than the systolic pressure. The usual method was to determine the point of palpatory obliteration of the pulse wave distal to the compressing arm band. The auscultatory method has, however, greatly simplified the accuracy of blood-pressure readings, and has gradually supplanted the palpatory method. The systolic pressure may be defined as the sum total of pressures existing in the artery under observation during cardiac systole. It is made up of the diastolic pressure existing in the artery during the cardiac pause or diastole plus the pressure or force exerted by the contracting ventricle in excess of the diastolic pressure. This latter, known as the pulse-pressure, represents the expenditure of force necessary to move the column of blood in the artery. It represents motion through the expenditure of kinetic energy. During systole, as the intraventricular pressure rises, the aortic valves do not open until the pressure at least equals the pressure then existing in the aorta, *i. e.*, the diastolic pressure. The ultimate or total pressure reached must be considerably in excess of the diastolic pressure, for if such a result were not attained at the end of systole there would be no pressure effective to promote blood movement. The pulse-pressure then represents the effective *vis-a-tergo* promoting blood movement. The pressure exerted by the cardiac systole up to the moment of opening the aorta valves avails the circulation nothing at all. It is, so to speak, kinetic energy wasted in overcoming static or potential energy. It is therefore the sum of the diastolic and pulse-pressures which go to make up what has been recognized as the systolic pressure.

The systolic pressure represents the total expenditure of kinetic energy on the part of the myocardium necessary to effect blood movement at a given moment. It represents heart work and is relatively a variable force, since the circulatory requirements may have considerable variation, dependent upon emotions, such as anger or anxiety, apprehension and nervous unrest, and upon physical stress and exertion, which may for the time being draw upon the cardiac reserve strength. It is a much more variable pressure than the diastolic pressure. An increased systolic pressure from this point of view means an increased cardiac expenditure of energy and nothing more, while a decreased pressure represents less expenditure of cardiac energy. The height of the systolic pressure in a compensated heart is dependent upon the height of the diastolic pressure (*i. e.*, the arterial tonus) to a large degree. But an increased systolic pressure may also depend upon certain factors, such as liver cirrhosis, mediastinal growths, pleuritic effusions, aortic aneurysm or incompetent heart valves, not necessarily associated with arterial hypertonus, but making necessary the expenditure of extra force in an endeavor to promote circulatory equilibrium.

The Diastolic Pressure. The diastolic pressure represents the more or less constant potential or static pressure existing in the artery under observation during the diastolic pause between succeeding systoles. The chief factor affecting this pressure is the tonus and degree of elasticity of the arterial wall. Of probably less importance is blood volume and viscosity. The following distinction may be made that while the total or systolic pressure represents cardiac force the diastolic pressure represents the resistance offered by arterial tonus. The diastolic pressure consequently should be taken as the index of arterial tension. A high diastolic pressure therefore means hypertension irrespective of the height of the systolic pressure, and *vice versa* a lowered diastolic pressure means hypotension, irrespective of the systolic pressure.

In an examination of over 500 individuals, for the most part below the age of forty years, who presented no symptoms of circulatory disease, I have found that the average diastolic pressure was between 80 and 85 mm. Hg. A persistent diastolic pressure of 100 signifies, in my experience, a mild degree of arterial hypertonus. If this pressure persistently averages 110 a more definite hypertonicity is present and usually signifies the beginning of an advancing vascular disease with contracted arteries. If a diastolic pressure of 115 to 130 is maintained persistently, definite vascular contraction has occurred. To this there are few exceptions. There have been occasional instances in which arterial hypertonicity of a temporary duration has occurred, due to toxemia, the result of a temporary hyperglycemia, or urea retention (as in acute nephritis). In these instances of temporary duration the diastolic pressure has fallen as the cause has been relieved.

When the diastolic pressure is maintained at a high level, from 130 to 160, the conditions are present which have so long been associated with contracted kidneys. The associated kidney disturbance is but an evidence of the vascular changes, the hypertonus and constriction, present throughout the circulatory tree. It does not follow nor has it been proved that the primary cause of the hypertonus is the result of altered kidney function. The kidney damage is probably coincidental to the vascular damage inflicted elsewhere through metabolic factors many times unknown, producing hypertonicity and constriction of the arteries. The essential point is that the diastolic pressure is the true index of arterial tension.

The Pressure-ratio.[13] With a heart possessing normal contractility and tonicity, so far as one may judge in the present state of knowledge, there exists within certain limits a normal ratio between

[13] In earlier papers dealing with this subject the term heart-load was used to designate the increased ratio between pulse-pressure and diastolic pressure found in the cardiac groups. Such a term while suitable for the cardiac groups is inadequate for the cerebrorenal group of hypertension, for while the ratio between pressures is usually within normal limits in this group when the heart is compensated, the heart-load or work is necessarily increased because the heart is contracting against an increased diastolic pressure. The term pressure-ratio is therefore to be preferred.

the diastolic and pulse-pressure. As has been before mentioned it is the sum of these pressures which make up the total or systolic pressure, so for practical purposes the systolic may for the time being be disregarded. In a study of about 500 individuals with supposedly normal hearts I have noted that the pulse-pressure averaged about 50 per cent. of the diastolic pressure. That is, with a diastolic pressure of 80 mm. the pulse-pressure was an additional 40 mm.; with a diastolic of 82 mm. the pulse-pressure was 41 or 42 mm.; while with a diastolic of 90 mm. the pulse-pressure was 45 mm. The normal pressure-ratio was therefore formulated as follows:

THE PULSE-PRESSURE DIVIDED BY DIASTOLIC PRESSURE or $\frac{\text{P. P.}}{\text{D. P.}}$

The ratio here given merely expresses the fact that under normal conditions, as well as in certain abnormal states in which the heart is in compensation, a pulse-pressure force 50 per cent. in excess of the diastolic pressure is required by the heart in systole before the aortic valves open and mass movement of blood is affected toward the periphery. The ratio also expresses the relationship between the kinetic energy expended by the cardiac contraction in moving the blood column and the potential energy or resistance offered by the arterial walls and volume of blood which they contain. This ratio may vary within normal limits between 40 and 60 per cent. The tendency toward this ratio is always evident with compensating hearts in pathological states with true hypertension due to an increased diastolic pressure (*vide infra*). In such cases, as the diastolic pressure increases due to vascular contraction and rigidity representing a true obstruction to cardiac output, the pulse-pressure increases, due to the expenditure of increased cardiac force in the endeavor to adequately supply the periphery with blood. The systolic pressure is consequently increased when the diastolic pressure is high if the heart is compensating for the increased circulatory load it is obliged to carry.

Strassburger[14] first attempted in 1905 to obtain a pressure-ratio as a means of estimating cardiac efficiency founded upon pressure variations. His ratio was obtained by dividing the pulse-pressure by the systolic pressure.

Tigerstedt[15] has also suggested this formula for determining the efficiency of the heart as a pump. His formula takes into account the factor of blood velocity as follows:

$$\frac{\text{Pulse-pressure} \times \text{pulse-rate} = \text{velocity}}{\text{Systolic pressure} \times \text{pulse-rate} = \text{work}} = \text{heart efficiency.}$$

$$\text{This is equivalent to } \frac{\text{pulse-pressure}}{\text{systolic pressure}} \text{ or } \frac{\text{P. P.}}{\text{S. P.}}$$

This formula appears objectionable for the following reasons: When the intraventricular pressure rises during cardiac systole

[14] Quoted by Barach and Marks, Arch. Int. Med., 1914, xiii, 648.

[15] Quoted by Hirschfelder, Diseases of the Heart and Aorta, 1910, p. 26.

the aortic valves cannot open until this pressure at least equals the diastolic pressure in the aorta. The intraventricular pressure up to this point does not affect blood movement at all, it being the pressure exerted by the myocardial contraction in excess of the diastolic pressure, *i. e.*, the pulse-pressure, which is useful for the purpose of blood movement during the cardiac systole. It therefore appears that the ratio of pulse-pressure to a diastolic pressure should be taken as an expression of the measure of work done by the myocardium in overcoming peripheral resistance.

The Differentiation of Certain Types of Hypertension. In applying the formula here given to a considerable number of patients manifesting symptoms of vascular disease it became at once apparent that certain groups could be differentiated. The differentiation depended to a large degree upon the height of the diastolic pressure and the relationship which this pressure appeared to bear to the pulse-pressure.

The Cerebrorenal Group of Hypertension. In this group were found the patients with evidences of damage to the arteries in general and to the kidneys in particular. When the damage had been long sustained the diastolic pressure was persistently high, and if the heart were able to compensate for the obstruction offered by the higher diastolic pressure the systolic pressure was increased in practically normal ratio. This group comprised those patients with chronic nephritis of the so-called diffuse or interstitial variety. Polyuria was practically always present. The quantity passed at night was increased. The specific gravity was low, varying between 1.005 and 1.015. Periodically abundant casts were found and serum albumin was present. Such damaged kidneys, as is well known, have difficulty in excreting urinary solids, and the tendency to urea retention in the blood was always marked. If the protein food intake was in excess of 75 to 100 grams daily the tendency to urea retention would many times produce an aggravation of the symptoms. This tendency was evident in many patients who followed a careful diet and whose daily intake of protein would not exceed 50 grams.

The main subjective symptoms were dyspnea usually on exertion, a feeling of pressure in the head frequently referred to the back of the neck, weakness, restlessness at night and unsatisfying sleep, vertigo, early morning headache wearing off by noon, mental confusion or lack of the usual initiative and ability for concentration. Retinal and subconjunctival hemorrhages occurred in about 10 per cent. of the patients. The diastolic pressure, as before mentioned, was high, varying from 120 to 165, while if the heart was able to compensate for the obstruction offered by the increased diastolic pressure, the systolic pressure was high also. The ratio, as before expressed, between the pulse-pressure and the diastolic pressure was in an average of many readings taken in 42 cases, usually within

the normal limits of 40 to 60 per cent. The average age of these patients was fifty-five years. The average systolic pressure was 200, the diastolic 132, the pulse-pressure 68, while the pressure-ratio was 51 per cent. Twenty deaths have occurred in the series of 42 patients, giving a mortality of 48 per cent. within the three years of observation. In this group of 42 patients observed over the past three years the nephritic damage appeared to be but part of the general vascular pathology. The kidney manifestations appeared to be incidental to the general changes, which may be designated under the heading of Vascular Disease. The kidney symptoms and the high diastolic pressures which accompanied secondary contraction of the kidneys appeared to be the result of unknown metabolic factors producing hypertonus and contraction of the peripheral arteries. These vessels were rigid, but they were also contracted and their lumen diminished. Such must have been the case or the diastolic pressure would not have been so persistently increased.

I have believed from earlier observations, as well as from this series of 42 cases, that the danger to such patients because of the high diastolic pressure lay more particularly in cerebral accidents such as hemorrhage or thrombosis or cerebral edema. The mode of death in the majority has convinced me that such is the case. I have therefore designated such patients under the cerebral or cerebrorenal group of hypertension, although the general term vascular disease covers the ground more adequately.

Cardiac symptoms were many times prominent features in such patients. In the majority of the patients of this group, cardiac hypertrophy had occurred as a result of increased work in pumping against the increased diastolic pressure. The laryngeal edema leading to a constant desire to cough, the dyspnea which was many times distressing, the edema of the extremities and of the base of the lungs and the gallop rhythm pointed to cardiac disturbance. Such cardiac manifestations seemed to occur because of myocardial fatigue, and in such instances the pressure-ratios showed alteration due to a decreased pulse-pressure. This resulted in a lower systolic pressure while the diastolic was less affected. This seemed to occur because of inability due to fatigue to furnish an adequate amount of pressure or force in excess of the diastolic pressure to affect normal blood movement and stasis resulted. In such instances decreased urinary output usually was present and the symptoms due to increased retention of urea in the blood occurred. When an efficient digitalis preparation was administered at the time of such symptoms two purposes were secured: (1) the heart acquired increased tonus and force, and (2) diuresis was stimulated. The systolic pressure soon approached its former normal high level and the diuresis washed out the retained urea from the blood.

A certain proportion of patients in this group, 10 per cent,

(2 out of 20), have died as the result of myocardial exhaustion, but the much larger proportion clinically suffered cerebral hemorrhage or thrombosis and edema as a part of what we have for so long considered to be uremia. Whether a cerebral or a cardiac death is more likely to occur would seem to depend to a large degree upon the localization of the vascular degeneration. The degree of degeneration does not seem to be the same throughout the arterial system. In one patient the cerebral vessels may have suffered more than the coronary. Much may depend upon the condition of the vessels from the effects of some previous disease, as syphilis or the acute infections, such as typhoid or rheumatic fever. Syphilis, as is well known, seems to have a predilection for the aorta, the aortic orifice and by contiguity the coronary orifices.

From the stand-point of pathological physiology the kidneys in this group have difficulty in excreting urea and non-protein nitrogen products of metabolism. Few of these patients die in anuria, however. There has always been evidence of some ability to excrete water unless obstruction had existed, such as an enlarged prostate or uterine fibroid pressing upon the ureters. From the anatomical stand-point thrombosis of, or hemorrhage from, the cerebral vessels frequently occurred. The two processes altered kidney function and cerebral vascular structure often appeared to go hand-in-hand.

From the stand-point of prognosis it appeared that the higher the diastolic pressure the greater was the danger of a cerebral death.

The Cardiac Group of Hypertension. The second group which was differentiated by the study of the blood-pressure ratio was the cardiac group. In this group, while the systolic pressure was in some instances as high as in those of the cerebral group, the diastolic pressure was, as a rule, but little higher than the normal. The pulse-pressure was in consequence much higher than normal and the ratio of pulse-pressure to diastolic pressure was much increased. An average of the systolic pressures in the 32 patients of this group was 178 while the diastolic average was 93. Instead, therefore, of a normal variation in the pressure-ratio of 40 to 60 per cent. the ratio was increased to 92 per cent. This increased load over the normal limits stamped the cases as cardiac. This group was largely made up of those patients manifesting cardiac symptoms without the clinical evidences of vascular disease and its associated nephritis. It comprised those with damaged valves, with aortic sclerosis, dilatation, or aneurysm, with liver cirrhosis, with gouty manifestations, with emphysema, with syphilis or an earlier history of lead poisoning, and those whose lives had been given to hard physical labor calling for unusual cardiac demands. The symptoms of nephritis were usually lacking in the patients of this group. Such albumin as was found occasionally to be present in the urine could be attributed to stasis. The symp-

toms, such as polyuria, the tendency to blood-urea retention, the low specific gravity, the showers of casts were conspicuous by their absence.

The main subjective symptoms were fatigue on exertion, anginoid pains in the chest, cardiac arrhythmias due to ventricular extrasystoles or auricular fibrillation, palpitation, and dyspnea. The heart was hypertrophied in about half of the cases and likewise the peripheral arteries were rigid to palpation, but *the essential feature was that the smaller arteries, although rigid and sclerotic, were much contracted or the diastolic pressure would have been increased.* The distinctive feature of this group was the low diastolic pressure as compared with the cerebrorenal group.

The increased pressure-ratio was maintained in the patients of the cardiac group with little variation, as a rule, while the heart muscle was in compensation. In fact, in many instances the early signs of decompensation were associated with a falling systolic pressure, the so-called "primary high, secondary low" sequence. Death occurred in most instances with the symptoms of a gradually failing heart muscle or, more explicity, the symptoms pointed to a cardiac death. The systolic pressure was high in this group when the heart was in compensation, because the arterial tubes were rigid and did not passively dilate during systole to accommodate the increased blood flow into them caused by the cardiac contraction.

The prognostic point of value in the cardiac group of patients seemed to be in the maintained height of the systolic pressure as an evidence on the part of the myocardium of compensation for increased work. A falling systolic pressure in the cardiac group of hypertension was of evil augery. It usually signified varying degrees of cardiac dilatation.

On the whole the prognosis was better in this group than in the preceding cerebrorenal group, with much higher diastolic pressures. Of the 32 patients, of an average age of sixty-two years, 8 have died within three years of observation, giving a mortality of 25 per cent. All have died a clinical cardiac death with one exception, in which the death may have been cerebral and in which autopsy was not permitted. In the patients of the cerebrorenal group there was not only the danger of cerebral hemorrhage, or of cerebral thrombosis and edema incident to the development of uremia, but also the possible danger of cardiac failure which occurred in about 10 per cent. of the deaths in that group. In the cardiac group the danger appeared to be entirely cardiac and the deaths which occurred, with possibly one exception, were due to gradual myocardial exhaustion or, more acutely, with dilatation and pulmonary edema, or to angina pectoris. The patients of the cardiac group appeared to be better risks for anesthesia by ether or by nitrous oxide-oxygen than those of the cerebrorenal group with high diastolic pressures.

The Pressure-ratio in Angina Pectoris. In angina pectoris so much apparently depends upon the patency of the coronary orifices and the rigidity or absence of thrombotic obstruction to the coronary arteries, as well as the condition of the root and the first portion of the aorta, that little might be expected from a diagnostic stand-point from the study of blood-pressure variations. I have at hand repeated observations covering 15 patients studied during the past six years; 8 are living and 7 have died in an attack. The average age of the living is now fifty-nine years, the average age of the seven who died was sixty-one years at death. There were 9 males and 6 females. The average systolic pressure of 14 of these patients was 179 and the average diastolic pressure 100. The pressure-ratio average was 80 per cent. The highest systolic pressure observed was 250 while the highest diastolic pressure was 140. The lowest systolic pressure was 115 and the lowest diastolic pressure was 40, which occurred in a patient with aortitis and dilatation with relative aortic regurgitation from stretching of the aortic ring. The average age of the 9 males at the time of their first attack was fifty-eight years, while the average age of the 6 females at the time of their first attack was sixty years. The youngest patient was forty-two at the time of his first attack while the oldest was seventy-three. Two of the patients, 1 male and 1 female, died suddenly during their attack from rupture of the posterior wall of the left ventricle into the pericardium. The walls of the ventricles showed evidences of an earlier hemorrhagic infarction about the points of rupture. Osler in the Lumleian Lectures of 1910 before the Royal College of Physicians mentioned one patient in whom the systolic pressure rose to 340 mm. during an attack of angina. I have come to regard with relatively greater seriousness the angina patients who have normal or subnormal systolic and diastolic pressures. Those in my experience who have had exalted blood-pressures have survived the longest.

The Pressure-ratio in Cardiac Lesions without Hypertension. This group comprised those patients with cardiac lesions whose systolic and diastolic pressures were not increased. It was made up of 20 patients with average systolic pressures of 118 and average diastolic pressures of 62. The pressure-ratio was therefore increased from the normal of 40 to 60 per cent. to 90 per cent. The greatest increase was found in 6 patients with aortic regurgitation. Their average systolic pressure was 140 while the average diastolic pressure was 40. The pressure-ratio was therefore greatly increased to 250 per cent. In no other chronic cardiac conditions with which I am familiar were so low diastolic pressures encountered as in aortic regurgitation. This point appeared to have diagnostic significance in the differentiation of cardiac murmurs.

In considering prognosis in cardiac lesions without hypertension from the stand-point of the pressure-ratio many instances were

observed in which a greatly increased ratio appeared to be compatible with a few subjective symptoms of decompensation. This was to be expected, since the greatly increased pulse-pressure was evidence that the myocardium was able to furnish adequate force to affect blood movement in compensation for the valvular disability. When the cardiac force became inadequate as the result of dilatation due to stress or overexertion, possibly from no more apparently serious an incident than severe paroxysms of coughing in an attack of bronchitis, the pulse-pressure was decreased and the symptoms of cardiac incompentency developed. This clinically signified dilatation, and has been observed in 16 patients. There was but little change in the diastolic pressure when cardiac dilatation occurred. The most evident change was the fall in pulse-pressure which produced a lower systolic pressure. The pressure-ratio was therefore diminished, the extent of which seemed to bear a direct relationship to the degree of myocardial embarrassment. In these 16 patients the pressure-ratio at the time of such disturbance varied from 11.5 per cent. to 30 per cent. When the systolic pressure tended to approximate the diastolic pressure the danger of cardiac failure was increased, since there was apparently insufficient force during systole to much more than overcome the diastolic pressure in the aorta, with but little pulse pressure useful to the movement of blood. As a result the cardiac and respiratory centers in the medulla suffered, and at the moment when insufficient blood supply reached them the exitus occurred.

The Pressure-ratio in Myocardial Exhaustion Due to Acute and Chronic Illnesses. In an acute illness, such as pneumonia, erysipelas, septicopyemia, or the early stage of typhoid, the diastolic pressure has a tendency to fall 5 to 10 mm. below its former level, due in all probability to the relaxing effects of the absorbed toxins, either upon the arteries directly or upon the vasomotor center. This results in an increase in the pulse-pressure and the pressure-ratio, for during the early stages of an acute infection the systolic pressure is usually sustained at or near its normal height. At least this usually occurs if the heart is capable of normal response. When the stage of heart embarrassment is reached in an acute illness, either from an abnormally high rate or perhaps from exhaustion in the endeavor to maintain the increased pulse-pressure apparently necessary to supply the periphery with blood, the systolic pressure begins to fall. The pressure-ratio is in consequence decreased. This decrease has appeared to bear a definite relationship in a considerable number of instances to the other clinical evidences of cardiac exhaustion. For example, in a patient ill for about two weeks with typhoid fever the systolic pressure was 118, the diastolic 80, the pressure-ratio 48 per cent. He developed bronchopneumonia the following day and the systolic pressure was 115, the diastolic pressure 60, the pressure-ratio 92

per cent. The following day the systolic pressure was 128, the diastolic pressure 102, and the pressure-ratio had fallen to 25 per cent, which was considered a serious sign. Stimulation in the form of caffein was administered in an endeavor to produce a corresponding rise in systolic pressure. The pulse rate was at this time 140 to 160. Six hours later the systolic pressure was 80 and the diastolic had fallen to 55. One hour before death the systolic was 80 and the diastolic 50. The pressure-ratio was, of course, of less prognostic importance than the fall of the systolic and diastolic pressures.

Numerous instances of this type could be given. In some of the instances a fairly good ratio between the pressures was maintained until very near the end under the influence of strophanthin intravenously, Nativelle's digitoxin, caffein, pituitrin, or adrenalin. The subsequent fall in pressures sometimes occurred very rapidly; in fact, the advisability of administering such marked cardiovascular stimulants has been questioned seriously in my mind in such instances upon the basis that it is possible, although one may not say probable, that exhausted heart and vessel tonus might have lasted longer had not the whip been applied so vigorously near the end of the race. This much may be said: when the diastolic pressure falls the vessel tonus has diminished; if the systolic pressure is maintained at near its normal level the heart is doing increased work because of the increase in the pulse-pressure, its ability to thus perform increased work depends upon its unknown reserve strength; should the systolic pressure begin to fall approaching the diastolic pressure the outlook is bad.

I have seen only one individual recover in an acute illness in which only ten to twelve points separated the systolic and diastolic pressures. In this instance a strong man suffered a mania at about the time his convalescence appeared to be established in typhoid. The systolic pressure during a few moments of quiet was 98 and the diastolic pressure was 88. He eventually recovered. One more instance of acute infection may be cited. A patient suffering with acute gangrenous stomatitis (Vincent's angina) and septicemia had early in her illness a systolic pressure of 120 while the diastolic pressure was 80. Five days later the diastolic pressure had fallen to 60 while the systolic pressure was maintained at 120. Two days later, with a pulse-rate of 140 to 148, temperature 103° to 104° (axillary), the diastolic pressure had fallen to 40 and the systolic pressure to 105. Death occurred about twenty-four hours later. She had taken 30 c.c. of a tincture of digitalis, the strength of which had been standardized by the cat method of Hatcher and Eggleston, during four days with no demonstrable effect.

In surgical shock in individuals with supposedly strong hearts the diastolic pressure was usually low. This was evident in repeated instances, especially if severe hemorrhage had occurred. The systolic pressure was usually maintained within normal limits so long

as the heart was able to sustain the greatly increased pulse-pressure, a fact in accord with the often repeated observation of Hürthle "that with a decreased peripheral resistance there is an increase in the pulse-pressure." Such increased work did not, of course mean increased output of blood moved by the heart toward the periphery, for the heart was pumping into more or less empty vessels if severe hemorrhage had occurred, or if venous stasis had resulted in the splanchnics. Its output was diminished because of lowered venous pressure on the right side of the heart while its futile work was increased until the point of exhaustion was reached when a fall in the systolic pressure occurred.

Crile in a preliminary note about twelve years ago mentioned the rise in systolic pressure which usually occurred with the onset of peritonitis. He did not refer to the diastolic pressure. In several instances which I have observed the systolic pressure was increased during the development of peritonitis and the diastolic pressure was also increased. For example, in a patient with acute miliary tuberculosis and intestinal perforation in which operation was not advised the systolic pressure was 120 and the diastolic 105 twelve hours after the perforation. Fourteen hours later the systolic pressure was 130 and the diastolic 110. Eight hours later the systolic pressure was 145 while the diastolic was 110. Sixteen hours later (four hours before death), with evidence of a rapidly failing heart and pulse-rate of 160, the systolic pressure was 98 and the diastolic pressure 85. The two pressures were approaching each other and the heart had apparently not much more force behind it in systole than was necessary to open the aortic valves against the diastolic pressure.

Peritoneal handling, incident to surgical procedure without peritonitis, has produced a rise of both the systolic and diastolic pressures in several patients. One example may be given to emphasize that such pressure changes do not necessarily mean peritonitis, for such might be suspected from leakage after certain operations. A young man with continued uncontrollable slight bleeding from a gastric ulcer had a systolic pressure of 120 and a diastolic pressure of 90. The following day gastro-enterostomy was done. The systolic pressure rose shortly thereafter to 150 and the diastolic pressure to 115. The day following the systolic pressure was 140 and the diastolic 110. His recovery from the operation was uncomplicated.

In chronic illnesses not associated with symptoms of vascular disease, which necessitated confinement to bed, such as organic diseases of the central nervous system, the systolic and diastolic pressures were usually within normal limits until the heart muscle began to fail. At such a time the systolic pressure began to fall and approached the diastolic pressure, the significance of which was not difficult to anticipate. Any marked fall in the diastolic pressure may not occur until near the end, at which time and in

some instances for twenty-four hours preceding it may be difficult, if not impossible, to secure definite pressure readings.

In the chronic severe anemias, whether secondary or primary, without evidences of cardiovascular disease, the systolic pressure was lower than normal for the age, while the diastolic pressure was markedly decreased. An average of the systolic pressures of 8 primary anemia patients with red blood counts varying from 728,000 to 1,000,000 per c.mm. was 105, the average of their diastolic pressures was 52. Such lowered diastolic pressures would be expected because of the thinner blood volume and relatively empty vessels. The pressure-ratio average in these patients was increased to 102 per cent.

Conclusions. From a study of over 150 patients manifesting various degrees of vascular disease and cardiac disability certain types of blood-pressure variations have been noted. The types for the most part may be grouped under the following heads:

1. *The cerebral or cerebrorenal type of hypertension,* which comprised those patients with vascular disease in which there were evidences of damage to the arteries in general and to kidneys in particular. A cerebral death occurred in a large proportion of these patients and the unfavorable prognosis seemed to depend upon the height of the diastolic pressure. In the patients of this group the arteries were rigid as well as contracted.

2. *The cardiac type of hypertension,* which comprised those patients without evidences of vascular disease and its associated nephritis. Death usually occurred from myocardial exhaustion. The arteries were rigid, but not contracted, or the diastolic pressure would have been increased. The prognosis seemed to depend upon the ability of the heart to sustain the increased systolic pressure as a purely compensatory measure.

3. *The Cardiac Type without Hypertension but with Increased Pressure-ratio.* This group comprised valvular and myocardial lesions which necessitated increased cardiac work. The prognosis seemed to depend upon the ability to sustain an increased pressure-ratio. Death when it occurred was due to myocardial exhaustion.

4. *The Cardiac Type without Hypertension but with Decreased Pressure-ratio.* This group comprised those patients with cardiac dilatation or those in whom marked evidences of myocardial exhaustion had occurred. The prognosis seemed to depend upon the reaction of the heart to stimulative measures in the endeavor to increase the pressure-ratio.

5. In general, it may be concluded from this study that too much reliance should not be placed upon blood-pressure variations as a guide to the condition of the circulation in any particular case, for such variations are of value only when associated with all other data. Certain groups of patients may, however, be differentiated in the manner above outlined, such differentiation possessing definite diagnostic and prognostic value.

VINCENT'S ANGINA.

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Certain anginas have been described by Plaut and Vincent as due to two organisms, one a fusiform bacillus and the other a spirillum, the two forms being considered either as stages in the life of one organism or as an example of symbiosis. The pathogenicity of these is still questioned in general, but especially often in particular. The difficulty of culture has prevented more frequent recognition, since smears are too rarely made. The ultimate test, namely, animal inoculation, has been remarkably unsuccessful.

The author once obtained from the peritoneal cavity of a sputum-injected mouse a smear which was typical for the average throat, and included Vincent's organisms. Pneumococcus Group II was obtained from the heart's blood. These results were never duplicated.

As to the occurrence of these organisms in general:

Berkeley speaks of their occurrence in healthy throats.

Bennerdoin found them in 64 per cent. of 227 cases of diphtheria, 73 per cent. of scarlet fever cases, 50 per cent. of streptococcic sore throats, 50 per cent. of cases of stomatitis, 67 per cent. of 31 cases of syphilis, 58 per cent. of 43 healthy cases.

Wingrave, who found them present in 80 per cent. of normal individuals, says they are frequently in nose discharges, in sinuses, in the tympanic cavity, etc. He denies their pathogenicity in man.

In 100 individuals having healthy throats, smears were made by the author, and in 43 per cent. Vincent's organisms were demonstrated. These individuals included nurses, patients, orderlies, doctors, and dispensary cases.

Leo Green speaks of Vincent's angina as occurring after measles, scarlet fever, whooping cough, and diphtheria. The late stages of severe cases are in reality the disease called noma. He reports an epidemic in a children's hospital as caused through the medium of a spoon.

Holstead reports it as a known specific cause of laryngitis, bronchitis, bronchopneumonia, mastoiditis, gangrene, ulcers of the penis and genitalia, abscesses, and general pyemia.

Tunnicliff and Wright report two cases of this variety of angina: the ulcerative or common form, and another the membranous or diphtheritic form. This is rare, occurring in 2 per cent. only of Rolleston's cases. In this latter form the bacillus alone occurs.

Rolleston considers the ulcerative as only the later stage. It would seem improbable, though not impossible, that were these organisms, which are found so frequently together in ulcerative conditions of the throat, purely saprophytic, in certain rare cases

one should appear to precede the other. It would seem that they represent stages of one organism, certainly the spirillum never appears alone, and the bacillus always develops first on culture media.

Green cured five cases with salvarsan, a known spirillicide. Unfortunately we do not know the effects of salvarsan in general in throat cases.

In the cases on which this article is based, smears stained with gentian violet were used in all. The diagnosis was made in three by a dark-ground illumination. In all smear-taking the necrotic material itself was obtained, as far as possible exclusively, and smeared. In one case an emulsion of this was injected into a mouse without result.

Of the 12 cases to be reported, 4 were individuals from whom smears had been taken previously in the study of healthy throats. Of these, 2 showed Vincent's organisms when in a healthy condition, and later suffered from a disease apparently due to these organisms. One showed it previously, but a later sore throat was streptococcic; and one having a smear negative for Vincent's previously, later developed a Vincent's follicular tonsillitis.

Case I.—C. J., angina, malaise. Temperature never over 99.4°. Deep ulcer under white necrotic mass. A diagnosis of syphilis was made. By dark-field illumination from smear following alcoholic application for one minute, and taken with the blood, motile spirillæ were seen varying somewhat in number and sharpness of curves, but all showed few and low curves. Bacilli were also seen. A smear showed the two organisms described by Vincent. The ulcer remained after all signs and symptoms had disappeared.

Case II.—Mr. M.; stiff neck first, four days later slight soreness in throat; never any other symptoms and never any fever. Left tonsil showed irregular white mass over easily bleeding ulcerous surface. A few white spots were on the other tonsil. White mass was hillocky and came off in pieces. Dark-ground examination of smear showed spirillæ as in Case I. Smear showed spirillæ and bacilli. Ten days from beginning the tonsil showed some white covered ulcers, but there were no general or local symptoms.

Case III.—Miss H.; sore throat; patches on right tonsil; headache. Temperature, 104°; malaise. Removed membrane. In two days better; fever down. On the fifth day after going out there were some general symptoms. Right tonsil showed follicular tonsillitis. Smear negative. Next day the tonsil was more covered; dirty white masses easily removed. Seemed like food particles. Dark-ground illumination showed a few spirillæ. Bacilli frequent. Diphtheria organism negative. Throat hardly sore. Temperature, 99°. Deep in tonsil was a white based ulcer with an intense red margin. The eighth day showed same throat condition without symptoms.

Case IV.—H. S.; child, aged five years. Illness began with swelling of lower jaw on the right side. Third day later found a large, white, irregular patch on the left tonsil. Right tonsil showed enlarged white follicles. Diphtheria antitoxin given as precautionary measure (6000 units). Temperature as high as 102°.

Fourth day was better. Membrane unchanged. Temperature, 102°.

Fifth day the membrane was unchanged. Temperature, 102°.

Sixth day the membrane was smaller; spots on right tonsil. Temperature, 102°.

Seventh day the membrane was much smaller. Temperature normal. Spots nearly gone.

Ninth day there was no trace of membrane.

Smear here showed almost exclusively Vincent's organisms. Diphtheria organism negative. Membrane was multicolored, dirty, high, irregular, rather loose, and a foul ulcer underlay it.

Case V.—Miss A. T.; nurse. Previously throat was positive for Vincent's organisms.

First day the throat was sore and swollen on the outside; not sore inside. Temperature, 98°.

Second day was the same. Temperature, 99°. Throat sore inside, (evening). Both tonsils showed thick, irregular white masses over ulcerated bases. Smears from white masses showed Vincent's organisms. Diphtheria organism negative.

Third day the soreness was greater. Temperature, 100°. (5000 units of antitoxin).

Fourth day the throat was a little better. Temperature, 100° at 8 A.M. and 101° at 8 P.M.

Fifth day was much better; throat swollen. Temperature, 99° at 8 A.M. and 100° at 8 P.M. Ulcers unchanged.

Sixth day was much better. Ulcers still present. Temperature at 8 P.M. 99.4°.

Seventh day the ulcers were less marked.

Case VI.—Miss S.; aged twenty years; nurse. Sore throat off and on for two weeks. Headache, malaise, etc.

First day the temperature was 102°.

Second day the temperature was 102.8°. Right tonsil showed three white patches, one far behind the pillar. Smear showed both organisms of Vincent's, especially bacilli.

Third day she felt well. Temperature was normal. Throat was unchanged.

This case showed characteristic lack of paralleling clinical signs and pathology, also predominating bacilli as in membranous type.

These six cases certainly suffered from diseases having the fundamental points in common:

1 Characteristic serious-looking ulcers with characteristic membranes.

2. Symptoms, especially sore throat, mild out of all proportion to pathology.

3. Return to perfect subjective health a considerable time before ulcer disappeared.

4. Predominance in each case of organisms described by Vincent.

5. In two by special therapy and in three by special diagnostic technic, diphtheria and syphilis were respectively ruled out.

The following cases are not typical or characteristic:

CASE VII.—H. W.; aged nineteen years. First day had sore throat; the membrane on both tonsils was soft and easily removed. Smear showed long rods in preponderance; no spirillæ.

Second day the temperature was 103°. Culture showed staphylococci.

Fourth day the membrane was gone. Temperature was normal. Smear showed a few typical spirillæ. This case included because of the characteristic picture in the first smear suggesting the bacillus of Vincent. The predominance of rods agrees with the assertions concerning the diphtheroid type of Vincent's angina.

CASE VIII.—D. W. Young girl, aged sixteen years.

First day had fever, chills, bone pains, sore throat, follicular tonsillitis. Temperature was 101°. Pulse, 120. Patches developed on enlarged tonsils, later small white spots on cheeks, gums, and tongue. These had red areolæ. From careful smears of the centers, practically, exclusively, Vincent's organisms were found.

Twelfth day was about well.

The following cases with Case 5 are taken in connection with the routine examination made previously for normal flora.

CASE IX.—Bertha; three weeks before a routine smear was negative for Vincent's.

First day had sore throat; malaise.

Second day the temperature was 102.4°. Tonsils were large and covered by large gray areas; pink bordered. Smear from membrane showed Vincent's organisms predominating. Diphtheria bacilli negative.

Fifth day was better. Temperature was normal. Tonsils were large; gray patches present. Injected mouse with emulsion of membrane without result.

Seventh day the membrane had disappeared.

Eighth day, bouillon culture of streptococci from throat injected into mouse without result.

CASE X.—Miss N.; aged twenty years; nurse. Two weeks previously Vincent's organisms were found. Used hydrogen peroxide as gargle t. i. d. for one week.

First day had sore throat. Smear (general) showed Vincent's organisms. Smear of membrane showed only streptococci.

Second day the temperature was 103.6°.

Third day the temperature was 102°.

Fourth day the temperature was 98.4°. Membrane unchanged.

CASE XI.—Miss M.; three weeks previously found Vincent's organisms.

First day the throat was irritated.

Third day had sore throat. Temperature, 103°. Tonsil showed white spots.

Fourth day the temperature was 100°. Tonsils large. Spots very small. Smear showed Vincent's organisms.

Evidently Vincent's organisms, frequently normally present, may be found in the general throat smear and at the point of disease, or only in the general smear, or only at point of disease.

Under the usual cultural conditions employed in laboratories making routine twenty-four-hour reports, a positive or negative diagnosis of diphtheria as based on the growth of the bacillus pure or predominating can be made. The value of such a diagnosis depends upon the degree of accuracy with which a portion of the membrane from the throat is removed by a practitioner, retained upon the swab without contamination, and directly applied to the blood serum.

Practically all, as is well known, contain staphylococci and streptococci. Staphylococci or streptococci cultured pure or nearly so from a piece of membrane, especially if its surface is previously cleaned, may be considered as pathogenic for the case.

Smears from a membrane often give a much more definite diagnosis, as lurking contaminating organisms cannot cloud the picture.

Reports of staphylococcal or streptococcal growths from swabs received indiscriminately would appear to be of no value. The same conditions hold for other organisms more rarely seen in the throat pathology, which are culturable on ordinary media.

Vincent's organisms cannot be cultured by the ordinary methods (aërobic). The small percentages, less than one, reported of Vincent's organisms in routine work are probably made from smears of material from throats applied to the surface of media in especially large masses, but they are not growths.

By smears a diagnosis can easily be made. A large percentage of normal throats contain these organisms, as in the case of streptococci, but by careful differential smearing a conclusion can be reached as to the bacterial content of the membrane. In the case of mailed swabs there is nearly as much a question as to diagnostic value, as in the case of streptococci and staphylococci. However that may be, such a diagnosis would be much more frequently made than is usually imagined.

Certainly in many serious-looking anginas if the causative organisms are not those of Vincent's, at least the predominance of the latter in the picture of a smear, appear to be a sure guide to a diagnosis of great importance, prognostically and economically. Until by animal inoculation or special therapy their pathogenicity is

repudiated or substantiated, the sooner this guide is properly sought for the sooner will an important advance be made in this branch of medicine.

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SOME FACTS AND FALLACIES CONCERNING ABDOMINAL ADHESIONS AND BANDS.

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AND

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With the continued development of abdominal surgery there has been an increasing appreciation of the importance of the normal activities and pathological conditions of the peritoneum. The recognition of gross lesions of this structure, such as the more evident forms of active peritonitis and the resultant inflammatory adhesions, antedates by far our knowledge of the conditions giving rise to them. The demonstration of the bacterial origin of peritoneal lesions and subsequent investigations as to the causation of such bacterial invasions have placed our knowledge of the more acute forms of peritoneal disease upon a firm basis.

A far more difficult problem presents itself when we consider peritoneal adhesions and bands for which it is impossible to ascertain a definite antecedent acute inflammatory lesion. The recognition of such structures is not a recent one. It has been stated that Virchow, in 1858, was the first to describe these structures more in detail, but at that time, of course, there was no basis for a correct opinion concerning their causation. For a long time after the beginning of abdominal surgery upon a larger scale the avoidance and treatment of acute peritonitis engrossed the attention of operators. Further and extended observation of early cases led to information concerning postoperative and postinflammatory adhesions and to efforts to determine their cause and to attempts at their prevention. A still later development of the matter was

an endeavor to understand the symptomatology and diagnosis of abdominal adhesions as apart from other lesions.

Finally the work of such men as Jonnescu, Lane, and Treves, several decades ago, called the attention of surgeons to the existence of various folds, bands, and membranes in relation to portions of the gastro-intestinal tract and to their possible importance. It remained for J. N. Jackson, in 1909, to bring to a definite standing in our minds the significance of certain pericolic structures or membranes, and following him many investigators and clinicians have endeavored to place upon a firmer basis our knowledge of this subject.

A great deal of confusion which exists concerning all these adhesions, bands, membranes, etc., may be obviated by the clearer grasp of certain fundamentals, and an effort to distinguish between various groups and varieties of these structures, instead of attempting to make one theory as to their causation explain every case.

All abdominal adhesions and bands may be grouped into two classes:

1. Those adhesions and similar structures whose character and location make it evident that they must have been the result of a definite attack or attacks of peritonitis of more or less severity.

2. Those structures in which some doubt may be entertained as to their formation as the result of a distinct peritonitis.

The former class gives us more data upon which to form a conclusion; the latter is the one about which the discussion among surgeons at present centers. Jackson himself has stated that he is in the dark as to the causation of the membrane named after him or Jonnescu; others have been more definite in statements as to their opinions.

Membranes and adhesions not frankly the results of a peritonitis may be again subdivided into:

(*a*) Structures whose character and location make it possible that they may be the results of fetal maldevelopment.

(*b*) Similar membranes in localities in which this causation is not so plausible.

The explanation of the existence of both of these types has been attempted upon numerous grounds. Briefly, they are:

1. The attempt to explain all or most of these formations on the basis of failure of the rotation or descent of the gut or an anomalous growth of the peritoneum and mesentery in the presence of normal rotation. While there may be some basis for this assumption in certain cases, it has appeared more than a coincidence to us that these bands or veils with their attendant symptoms should be so often localized at or near that portion of the gut where we are most likely to have lesions of an inflammatory nature. Nor is it a counterbalancing fact that there is not to be found the remaining proof of such an inflammation.

Eastman, in experiments on rabbits, by artificially producing coprostasis, has succeeded in producing a low-grade peritonitis and subsequent formation of membranes. Cheever is one of those who dissent most strongly from this view of the matter, and his dissections somewhat strengthen his position. Nevertheless the experiments mentioned and those of Murphy and others on intestinal obstrucion lead us to the belief that in many cases a migration of bacteria through the intestinal wall can and does give rise to diffuse peritoneal inflammation of a low grade which results in the formation of veils, membranes, and bands.

It is a remarkable fact that these structures are most often found in adult life and at that time give rise to symptoms. Is not this also an evidence that an early underlying cause gives rise to conditions which cause their symptoms later, when the membrane or other structure becomes of such extent as to seriously interfere with the activity of the gut?

Granting at once that certain of the structures might possibly be the results of causes unassociated with inflammatory changes, there is no evidence that this is the case, and it is far more reasonable to suppose them the results of an inflammation until the reverse is proven.

2. Mr. Arbuthnot Lane and others (Fagge, etc.) have attempted to explain peritoneal bands as "crystallization of lines of force," and the result of stress upon normal structures causing them to be altered. There is no doubt that malposition of abdominal viscera must bring with it a malposition of their surrounding structures and coverings, but the whole of Mr. Lane's explanation of these conditions is surrounded by a haze of theory, argument, and supposition unsupported by facts. His theories are curious and interesting, but entirely unconvincing; plausible on first reading but not susceptible of close reasoning. Some of his views and statements do not bear analysis at all; their true inward meaning must be known only to Mr. Lane himself. To explain a definite and often pathological structure upon such vague and fanciful grounds does not tend to clarify the situation; it only introduces an additional mystery to a difficult subject.

3. In contradistinction to these views there are those who would explain practically all of these new or malformations of the peritoneum as the results of inflammation. It is a matter of no great consequence that many of these adhesions or bands are or seem to be congenital. The evidences of antenatal inflammation of the peritoneum are sufficiently definite in numbers of reported cases (Doran, Kieth, Ballantyne, and Veszprenit). It is the opinion of these men that such instances of fetal peritonitis as they cite are by no means uncommon, and the examples given are those in which there was no evidence of a purely mechanical origin of the peritonitis such as a perforation. The transmission of toxins and drugs from

mother to fetus is universally acknowledged, as is the transmission of the infecting agents themselves by means of the blood or indirectly through the fetal appendages (Burnet).

Since then the existence of not infrequent antenatal peritonitis is proven, we believe that those adhesions which are found not to have been caused by a peritoneal inflammation after birth are the result of a similar condition in the fetus; that whereas many of these adhesions are congenital they are not developmental in origin. It must be understood that from such an origin we exclude those instances in which there is but an accentuation or simple enlargement of a peritoneal membrane, fold or process normally present.

In taking inflammation, acute or subacute, as a causative factor of a condition, we are dealing with a fundamental entity, a condition with the results of which we meet every day. In assuming developmental errors as causative factors of lesions evidently pathological, we can only adopt the absence of other demonstrable causes as proofs of a supposed cause.

A consideration of the opinions of various clinicians and experimenters makes evident the fact that there is no agreement concerning these bands of membranes.

Fallon even states that Jackson's membrane is always present, and is a normal structure. With this view we are not at all in agreement. Lynch, after citing certain facts to prove that Jackson's membrane is not of inflammatory origin, concludes "that the membrane described by Jackson is of embryonal origin, but it may be so altered by inflammation as to appear like an ordinary adhesion." It may be embryonal and nevertheless inflammatory, and to distinguish between a membrane of inflammatory origin—antenatal or postnatal—and a membrane merely altered by an inflammatory process appears to us to be impossible.

We think there is every reason to believe that practically all of these structures are the result of peritoneal inflammation of some kind; and, moreover, we are convinced that more extended clinical observation on the part of those who have had greater opportunities to theorize about than to observe these formations can only serve to make them agree with this opinion.

Concerning adhesions which are frankly the result of one or more attacks of peritonitis after birth a great mass of literature has been accumulated. We believe that the fact is often lost sight of that such adhesions are principally an effort of nature to effect a cure or to limit infection. The various attempts, hitherto unsuccessful, to avoid such adhesions in inflammatory cases we believe to be efforts in the wrong direction. On the other hand, in clean cases in which infection plays no part, it is essential that by minimizing handling and exposure of the viscera we avoid the formation of adhesions of no value and possibly of great harm.

In conclusion, we would merely mention the increasing recognition

of the importance of abdominal adhesions, and our progress in their diagnosis is especially by means of the roentgen-ray. A less pleasing subject for our contemplation is our inability effectually to deal with such adhesions when they do exist and cause symptoms.

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THE TREATMENT OF SYPHILIS OF THE CENTRAL NERVOUS SYSTEM WITH INTRASPINAL INJECTIONS OF MERCURIALIZED SERUM.

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Until recently the treatment of syphilis of the central nervous system was not essentially different from that of syphilis elsewhere in the body. Because of this, results in these cases have been far from satisfactory.

Since the discovery that the Spirocheta pallida are the active agents and are found viable in the tissues and exudates in the so-called parasyphilitic diseases, the tendency has been to consider these cases merely cerebrospinal syphilis and to lose sight of the finer anatomical localizations. This also is in part due to the rapid advance in our laboratory methods.

Ravaut was the first to call attention to the diagnostic importance of a meningeal reaction in the very earliest stages of syphilis, which was too slight to be detected in any other way, except by the examination of the cerebrospinal fluid. Udo Wile, in this country, has been very active in substantiating this work of Ravaut's. This can mean only one thing—that the central nervous system is involved in the early stages in the majority of cases. Systemic treatment here is usually quite efficacious, even though there may

be an extensive meningitis, with headache and other functional disturbance.

Later, however, the changes in the central nervous system and its envelopes are more chronic and yield less readily to medication.

In the different anatomical types of nerve syphilis, such as the interstitial, the parenchymatous, and the essentially vascular, treatment will or will not yield results, depending on the accessibility of the diseased region to the medication. In the interstitial type, which includes meningitis luetica, meningo-arteritis, and gummata, the results from systemic treatment have been good, because symptoms arising therefrom have been functional and depend on the amount of exudate and pressure, the resolution of which often yields brilliant functional results. When, however, the nerve tracts or centers have been destroyed, full restoration of function cannot be expected.

In the parenchymatous type, which includes the so-called parasyphilitic diseases, irritation and destruction of nervous elements seem to be the essential features. Here, results of systemic treatment have been somewhat disappointing, except when the irritative symptoms have been due to active inflammatory processes.

The seat of the active lesion in most cases of tabes, namely, radiculitis, probably explains why some cases yield to the treatment better than those of general paresis, in which the spirochete and round-cell infiltration are scattered throughout the cerebral cortex.

Swift says of this: "The separateness of the dorsal roots may result in greater accessibility to the remedial agent, and it is conceivable that if all the radicular nerves and dorsal ganglia were gathered in one area, as in the cerebral cortex, the arrest of tabes might be as unsatisfactory as is the treatment of paresis."

Before the advent of salvarsan, treatment of nerve syphilis with mercury was far from encouraging because there were so many relapses. The present drift of opinion is that in the exudative, inflammatory, gummatous, and arterial forms, salvarsan is by far the most efficient remedy we possess. Schaller, as early as 1912, states in his conclusions that "the relief obtained from one intravenous injection of salvarsan appears to be temporary in the majority of cases."

Since large and more frequent doses have been given there are fewer neurorecidives and fewer relapses.

The use of salvarsan, which at first promised to yield such brilliant results, has in many cases, even with prolonged treatment, not given the expected results.

Just why was this? One or two answers suggest themselves—either irreparable changes had taken place in the nervous system or the drug failed to reach the seat of infection. Careful chemical investigations of the cerebrospinal fluids have shown no trace of

arsenic after the intravenous administration of neosalvarsan, and only very slight traces after salvarsan.

Swift and Ellis, in this country, conceived the brilliant idea that the administration of a salvarsanized serum into the subarachnoid space itself would possible alter some of the local conditions which were evidently not reached by intravenous administration.

The results of their studies are manifold. Reports of patients who were quickly relieved began to appear. Some observers questioned the efficacy of the method, arguing that the cause of the improvement in clinical symptoms was the intravenous administration, and not its local application, and that the improvement in the cerebrospinal fluid findings was due to the withdrawal and subsequent dilution of the remaining fluid by the injected serum. Sachs, Strauss, and Kaliski have shown that up to forty-five minutes after the administration of 0.6 gm. salvarsan intravenously, only from 0.00004 to 0.0001 gm. of metallic arsenic could be detected in 20 c.c. whole blood; after forty-five minutes practically no free arsenic could be demonstrated.

Other workers, especially Marinesco and Ravaut, injected unchanged neosalvarsan in aqueous solution into the subdural space, but the reactions were severe and the results doubtful.

Great caution has to be exercised in the use of these unstable arsenical preparations, because of their irritative and toxic properties. This was shown in the very unfortunate circumstance which happened on our coast some months ago.

Ravaut, in 1913, had treated two cases of cerebrospinal syphilis with injections of mercurial salts into the subdural space, with marked improvement. Neither case had been followed more than a few weeks. Byrnes, in 1913, believed that many patients who were receiving the Swift-Ellis treatment were also being actively treated with mercury. In those patients who were receiving mercury, especially the inunctions, the presence of mercury (0.0000059 gm. per c.c.) could be demonstrated in the serum, an amount equal to the salvarsan content of salvarsanized serum, so that these patients were receiving a mercuralized as well as a salvarsanized serum.

Byrnes used, in general, the Swift-Ellis technic for the preparation and administration of the serum, except that no drug was administered before withdrawing the blood.

The preparation of patients and technic of administration of the serum in the cases reported below are essentially that of Byrnes' original procedure.

1. For one week the patient is given full doses of mercury, preferably 1 dram of the ointment inuncted every night.

2. Forty c.c. blood are collected in dry sterile centrifuge tubes. The blood is centrifuged immediately and then placed in a

refrigerator for eighteen to twenty-four hours when it is again centrifuged for fifteen or twenty minutes and 18 to 20 c.c. serum are pipetted off.

3. One c.c. of a solution of mercuric chloride in distilled water, which contains $\frac{1}{50}$ of a grain of bichloride, is added to the serum.

4. This prepared serum, which should be perfectly clear, is then heated at 56° C. (132° F.) for half an hour.

5. A lumbar puncture is performed. Spinal fluid is removed until the pressure reads about 30 mm.

6. The prepared serum is slowly administered by gravity, at body temperature.

7. The patient is placed in a bed, the foot of which is elevated eight inches, for four hours.

8. Liquid diet is ordered.

9. Morphin sulphate (gr. $\frac{1}{4}$) is prescribed if necessary.

Difficulty in getting clear serum which contained no hemoglobin was encountered at first, but since all apparatus used is perfectly dry, there have been no severe reactions, which will be described in one or two of our earlier cases.

For determining the efficacy of this method I have determined to apply it for certain indications, only general paresis and in tabetics suffering from lancinating crises in the legs. Since gastric crises may be due to causes extra spinal, *i. e.*, disease of the sympathetic, it was decided not to treat tabetics with the latter manifestation as the only complaint by this method.

Twenty-five patients have been treated by this method in the last seven months—125 injections form the basis of this report. On an average, 5 injections were given each patient. One to two weeks' interval elapsed and all reaction had entirely subsided before a second injection was given in any case. A report of the more interesting cases follows. In all there were treated: Erb's syphilitic spastic spinal paralysis, 2 cases, 6 injections; general paresis, 3 cases, 15 injections; tabes dorsalis, 20 cases, 104 injections.

The luetin was done on patients having had no potassium iodid before or during the test. Detailed report of the most instructive cases follows.

Case I.—Erb's syphilitic spastic spinal paralysis.

E. H., aged forty-one years; German. Entered the San Francisco Hospital September 24, 1914, complaining of inability to walk.

The patient had had gonorrhea in 1903 and a primary sore in 1908. The onset of his present trouble dated from 1912, with paresthesia of the buttocks, as if he were sitting on something cold. Pain in the left ankle soon followed. Six months later he suddenly lost the use of both legs. This lasted seven months, when slight power returned so that he could get around with the use of two canes. One year later a relapse occurred. During this time he was given five salvarsan injections and many mercurial rubs. No

marked improvement. Examination at this time showed a spastic paraplegia with marked weakness of the quadriceps extensor and the peroneals. The adductors were spastic.

Slight deafness in the left ear; pupils equal and react actively to light.

Reflexes: Knee-jerks, right and left, both exaggerated. Ankle-jerks exaggerated.

Babinski positive, right and left. Right superficial abdominals left.

Bathy anesthesiæ of both big toes. No marked sensory involvement elsewhere.

Marked pains encircling lower abdomen were present. Much incontinence of urine, especially at night.

Merc. serum.	Date.	Cerebrospinal fluid.			Wassermann.			Reaction.	Remarks.
		Pressure.	Cells.	Albumin	Blood.	C. S. F.	Luetin.		
I	Mar. 27	280	200	+	−	−	+	To 104° vomit headache	Bloody serum.
II	May 19	?	80	Slight	−	−	−	None; temp. 102°	Better control of urination; pains disappeared.
III	June 17	130	38	−	−	−	−	No reaction; temp. 100°	Complete control of urine. No pains.

The reaction was very severe after the first treatment, due to contamination of the serum, with hemoglobin. This patient after the second injection had no further girdle sensations or pain in the legs. The bladder gave much less trouble. He, however, has no better use of his legs since the treatment.

Case II.—*Tabes dorsalis.*

H. M., aged forty-nine years; electrician.

Entered the San Francisco Hospital July 1, 1915, complaining of general weakness and dizziness.

Gonorrhea and probable chancre thirty-three years ago. Some alcoholism. Onset of present illness occurred about fifteen years ago, when the knees began to give out. This was followed by a dead feeling in the legs, with inability to walk in the dark. Early fatigue was marked. Severe pains in the legs and around abdomen supervened which were present on admission. Patient had been a sufferer from biliousness for many years.

Examination showed marked bilateral deafness (catarrhal?).

Argyl-Robertson pupils; punched-out scars on shins.

Hypesthesia of the legs; absent knee and Achilles jerks. Ataxic gait; Romberg positive.

Bladder crisis and polyakiuria.

Blood Wassermann negative; luetin positive.

Merc. serum.	Date.	Cerebrospinal fluid.			Wassermann.		Reaction.	Remarks.
		Pressure.	Cells.	Albumin	C. S. F.	Blood.		
I	July 24	?	5	+	+++	− − −	Very slight	Bladder, pain still continues.
II	Aug. 8	185	18	+	−	Luetin +	Very slight	Band-like sensations around abdomen. No pain—biliousness.
III	Sept. 5	135	8	−	− − −	−	No reaction	Weakness. No pain.
		No previous treatment						
IV	Oct. 10	140	4	−	− − −	−	No reaction	None.

CASE III.—*Tabes dorsalis.*

W. H., carpenter; aged forty-eight years.

Entered Hospital July 23, 1914, with "rheumatism."

Neisserian infection; 1901, painless sore on penis at same time.

Moderate use of alcohol. Excessive tobacco.

Onset of present illness in 1902, with staggering in the dark.

Marked attacks of nausea and vomiting, with loss in weight and pains in legs.

Examination showed Argyl-Robertson pupils; loss of knee-jerks and ankle-jerks; extreme ataxia and positive Romberg.

Anesthesia of skin of legs and about nipples.

The patient was given two doses of Salvarsan, and mixed treatment, which always disagreed with him.

Fraenkel movements were instituted with good results.

Blood Wassermann + + +.

Merc. serum.	Date.	Cerebrospinal fluid.			Wassermann.		Luetin.	Reaction.
		Pressure.	Cell.	Cell.	C. S. F.	Blood.		
I	Mar. 28	?	31	?	+++	+++	+++	Marked gastric crisis.

Crisis lasted seven days; two small ones since for short time.

Ataxia improved; no pains. Patient had a mild gastric crisis three days one month later.

CASE IV.—*Tabes dorsalis.*

R. W., aged forty-five years, machinist.

Entered hospital December 9, 1914, because of pains in legs and inability to walk.

Gonorrhea and chancre in 1905; no secondaries.

Onset of symptoms, 1907, with numbness in legs followed by staggering at night, especially. Shooting pains in the legs developed. No girdle sensation at first. In the last two years condition became extreme, so that he was taking opiates about 1 grain per day. During this same time patient had four full doses of salvarsan and continuous mercurial treatment.

Examination showed extreme ataxia, positive Romberg; absent knee and Achilles jerks; Argyll-Robertson pupils.

Loss of pain touch and temperature sensibility in legs and abdomen. Hypercryalgesia in the back.

Fraenkel movements were started January 2, 1915, but discontinued because of the pain.

Two doses of neosalvarsan were given on January 7 and 14.

Blood Wassermann + + +.

Merc. serum.	Date.	Cerebrospinal fluid.			Wassermann.		Luetin.	Reaction.	Remarks.
		Pressure.	Cells.	Albumin	C. S. F.	Blood.			
I	Feb. 4	265	40	+	− − −	+++	+	.....	Contamination; hemoglobin.
II	Feb. 18	125	40	+	− − −	....	...	.....	Pupils sluggish; pains disappeared.
III	Apr. 17	125	3	+	− − −	....	...	Slight reaction	Fränkel movements continued.

Remarks: No pains since second treatment; restraint.

CASE V.—*Tabes dorsalis.*

W. M., aged thirty-six years; cabinet-maker.

Entered the hospital April 12, 1915, because of pains in the legs and loss of use of the legs.

Denies lues but admits two Neisserian infections fourteen years ago.

Eight months before admission had soreness and stiffness in legs on walking, so that soon he had little use of his legs. This was accompanied by great shooting pains in the legs and back. Bladder incontinence with dysuria developed.

Examination disclosed Argyll-Robertson pupils; absent knee-jerks and ankle-jerks; disturbed sensation in legs and nipple region.

Marked ataxia and positive Romberg.

Blood Wassermann negative; luetin +.

Cerebrospinal fluid: Wassermann negative.

Mercurial and three salvarsan treatments made no impression on the pains and bladder trouble. The result of treatment by mercurialized serum is shown in the table on page 272.

These cases illustrate in general the results which have been attained. In these 25 selected cases all have improved considerably even when other treatments were totally unavailing.

With improved technic the reaction following the first injection is very slight and consists usually of increase in the pain, slight dull headache, a temperature rising to 99° or 100° and perhaps slight nausea, all of which disappear in eighteen to thirty hours, and are easily controlled by opiates. Subsequent injections cause little or no reaction.

Merc. serum.	Date.	Cerebrospinal fluid.			Wassermann.		Luetin.	Reaction.	Remarks.
		Pressure increased	Cells.	Albumin	C. S. F.	Blood.			
I	May 17	?	100	+	– – –	– – –	+	Severe headaches, temp. 102°. Nausea	
II	June 3	?	12	?	– – –	....	...	Very slight headache and pain in legs. Temp. 98°	Bladder symptoms improved much.
III	June 16	?	17	–	Doubtful	....	...	Moderate reaction; pain in legs and hips. Headache. Girdle sensation.	Pain disappeared in twenty-four hours.
IV	Aug. 14	....	25	?	– – –	....	...	Very slight; 101°; slight headache	Great improvement in ataxia. No pain in legs.
V	Sept. 10	140	10	–	– – –	....	...	None	Bladder O. K.
VI	Sept. 24	....	8	–	.....	....	...	None	

Table showing result of treatment by mercurialized serum in Case V.

In the last 100 injections there has been practically no more reaction to the injection beyond that which would occur in any lavage of the subdural space.

Patients originally suffering from gastric crises usually had a severe crisis precipitated by the injections, although there were fewer and less severe crises following in one or two cases. These cases will be studied further. No sphincter disturbances were noted in any case. These are occasionally seen after the Swift-Ellis treatment.

It is important to examine the urine for abnormalities before each treatment, as the presence of albuminuria is, I believe, a distinct contra-indication for treatment.

In 85 Swift-Ellis treatments which I have done there has been no such marked improvement in clinical condition so early, as after the mercurialized serum is given. Occasionally a patient will have a severe outburst of pain, which is of very short duration, in the interval between treatments.

In the first case mentioned the bladder disturbance entirely cleared up after the second injection. The cellular contents of the spinal fluid rapidly diminished with the treatment in cases in which an abnormal count was found.

Conclusions. The facts of greatest interest to the neurologist in connection with the intraspinal mercurialized serum treatment are:

1. There is no danger in its administration.

2. For local treatment it is very efficacious in syphilis of the central nervous system, especially in the treatment of tabes dorsalis, in which lancinating pains are the predominant symptom.

3. Due to its stability the serum may be used at any time after its preparation.

4. The lack of expensive drugs used in its preparation makes it invaluable at this time.

5. There is no objection to a combined salvarsanized and mercuralized treatment.

6. It must not be concluded from the short space of time (eight months) that has elapsed since the beginning of this form of treatment in these cases that relief is going to be permanent. One will have to be cautious about prognosticating a cure until the proper length of time elapses, *e. g.*, at least three years. From the results obtained so far it certainly has mitigated the symptom of pain.

HEMATEMESIS DUE TO CHRONIC APPENDICITIS, WITH AN EXPLANATION OF ITS PATHOLOGICAL PHYSIOLOGY.

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The patient was a male, aged fifty years, by occupation a farmer. He was always well up to ten years before operation, although he has always been severely constipated. This began to be progressively worse at this period. He never had a definite attack of colic or acute abdominal illness.

Five years and a half before the operation he consulted a competent gastrologist, whose records we have been privileged to examine. The principal complaint was constipation and sour stomach, with eructations of acid material. Vomiting was not present to any extent. There was pain in the epigastrium before and after meals. He had never vomited blood except a few times after prolonged hiccoughing spells, which he often had. An examination of the stomach contents at this time discovered hyperacidity and hypersecretion. He was treated for a time, and was well after going home for about a year, when the same symptoms returned. He was treated by various methods with only temporary relief for about four years, when he presented himself for operation, advised by the gastrologist who had formerly examined him.

He had lost a few pounds in weight. The prominent symptom was still epigastric pain and recurrent vomiting. Two weeks before he had vomited twice, bringing up a pint of dark red blood each time. He was not jaundiced. There was considerable rigidity along the right rectus muscle and tenderness over the epigastrium, under the right ribs and in the right iliac fossa. He was given a test meal. He

returned for its removal a half-hour after the appointed time, but, nevertheless, the stomach tube brought away over a pint of highly acid material. The test for blood by Mayer's solution was positive. The diagnosis of pyloric ulcer and stenosis was made.

At operation an incision was made high up over the edge of the right rectus above the umbilicus. The gall-bladder was empty of stones, with thin walls, and easily emptied by pressure. The stomach had no sign of ulcer, no scar, no dimpling, and the pylorus was patent. The surface of the gastric serosa around the pylorus was reddened and mottled with small veins like a drunkard's cheek. The veins in the region were distended and tortuous, and in the mesentery along the greater curvature were numerous small, hard, shot-like glands.

On investigating the appendix it was found buried in a dense mass of adhesions, from which it was removed with great difficulty; in its mesentery were found several lymphatic glands the size of peas, one or two of which were removed for microscopic examination.

The ascending colon was enclosed in a veil of rather dense membranes, which extended across it from the abdominal parietes.

The appendix was removed and the abdomen closed. No attention was paid to the membrane on the ascending colon so far as operative measures were concerned.

One year after operation the patient's condition was good. He was free from the epigastric pain and hyperacidity, had never vomited since the operation, and his constipation was much better. He had gained ten pounds or more in weight.

Upon this history we desire to make several comments: Gastric hemorrhage in appendicitis has been described by Moynihan,[1] La Roque and several other authors, and since attention has been directed to it has been found by many surgeons of experience. No explanation of its cause has, however, so far as we are aware, been offered in print.

In the present case the first thing which should be emphasized is there is no possible doubt that a true inflammation of the appendix was present. The changes found were definite and evident to everyone who saw them. The evidence necessary to convince some surgeons that an appendix is diseased is often of the flimsiest nature: it may be too short, too long, too pale, or too red; the slightest kink may be pointed out as the cause of a hideous train of symptoms. In this case, however, the enlarged glands in the mesentery of the appendix, which were of enormous size, were objective evidences which could be seen, handled, and weighed, and are undeniably signs of chronic inflammation. Added to these is the heavy mass of adhesions around the appendix, the attachment of the mesentery, the constriction of the lumen, and the obliterating fibrosis seen in the sections.

[1] Brit. Med. Jour., January 29, 1910.

Next in importance are the changes observed in the serous covering of the stomach and the structure of the omentum and gastrocolic mesentery. The innumerable small glands in the omentum and mesentery, hard and universally distributed, pointed to a stream of infection carried up the omentum and deposited at the pylorus. The appearance of the stomach, mottled and covered with fine veins, was the evidence of the result of this bombardment of septic material.

The hemorrhage of the stomach was almost certainly due to the seepage from this inflamed gastric mucosa and serosa rather than any rupture of an enlarged vessel. The dyspepsia, the hyperacidity, and the epigastric pain were the reaction of the stomach to this continuous stream of irritation passing from the appendix up the omentum, which it will be remembered was attached directly to the appendix, to the organ which forms the attachment for the omentum —the stomach.

This, at least, is our own explanation. It explains not only this case but the many cases of dyspepsia exactly simulating the symptoms of gastric and duodenal ulcer in which no ulcer is found, but which in many cases when the appendix looks innocent enough are cured by an appendectomy.

May it not be possible that perhaps many cases of gastric or duodenal ulcer have their origin in a chronic appendix, that the ulcer may be the site of a septic embolus which has traveled along the omentum from a diseased appendix? We have no experimental evidence but abundant clinical reason to believe so.

Owing to the mistake in diagnosis in this case we were afforded an unusual opportunity of examining other organs besides the offending appendix. In most operations done for chronic appendicitis the incision is made low and no inspection of the stomach can be made: on the contrary, in many cases of gastric ulcer or cholecystitis no examination of the appendix is made. Moynihan in recent articles states that in all of his later operations for gastric or duodenal ulcer he examines the appendix and finds it diseased in the vast majority of cases.

Finally, this case is suggestive in another way: In looking over our past records we have noted two cases which were operated for gastric hemorrhage. The records state that no evidences of ulcer were found in either case. In both the stomach was opened and an inspection of the mucosa revealed a red, inflamed surface. Punctate points of hemorrhage were seized with forceps and ligated. No examination of the appendix was made in either case. It was designed at one time to group these cases and report them under the title "Idiopathic Gastric Hemorrhage." We now believe they were both due to chronic appendicitis.

REVIEWS

A Manual of Chemistry. A Guide to Lectures and Laboratory Work for Beginners in Chemistry. A Text-book Specially Adapted for Students of Medicine, Pharmacy and Dentistry. By W. Simon, Ph.D., M.D., late Professor of Chemistry in the College of Physicians and Surgeons, Baltimore, and in the Baltimore College of Dental Surgery; and Daniel Base, Ph.D., Professor of Chemistry in the Maryland College of Pharmacy, Department of the University of Maryland. Eleventh edition. Pp. 648; 55 illustrations. Philadelphia and New York: Lea & Febiger, 1916.

The approval of and the demand for the book is shown by the fact that it is now in its eleventh edition. Its object is "to furnish to the student in concise form a clear presentation of the science, an intelligent discussion of those substances which are of interest to him, and a trustworthy guide to his work in the laboratory." The work is comprehensive and fulfils the requirements of all those concerned with the medical aspects of chemistry. Changes in and additions to the new *United States Pharmacopœia* have been incorporated. In the section devoted to analytical chemistry a chapter on quantitative determinations by volumetric methods has been introduced. That part dealing with non-metals has been rearranged and much new material has been added. In Section I, on Physics, the chapters on light and electricity have been omitted because of their slight bearing on a course in elementary chemistry. This is particularly advantageous, in that it leaves the mind free to grasp the more important fundamentals having a distinct bearing on the work at hand. For a somewhat similar reason it might perhaps have been better to retain in full the section on Physiological Chemistry, since its importance justifies what may in some instances be a repetition of work already studied. Altogether, the change in the grouping of subject matter is a desirable one. Section I treats of chemical physics; Section II deals with the general chemistry of the non-metals and of the metals and their combinations; Section III is given over to analytical chemistry, while Section IV is devoted to the essentials of organic chemistry. The articles on the polariscope and spectroscope have been placed in the Appendix.

The view, as expressed on page 506, that inosite, $C_6H_6(OH)_6$, is a hexahydroxybenzene, is no longer tenable. In the light of our present knowledge, inosite is to be regarded as a hexahydroxyhexamethylene, presumably formed from carbohydrates.

On the whole, this new edition is up-to-date and will continue to be accorded the approbation gained in the past. H. D.

A Text-book of Practical Therapeutics. By Hobart Amory Hare, B.Sc., M.D., Professor of Therapeutics, Materia Medica, and Diagnosis in the Jefferson Medical College; One Time Clinical Professor of Diseases of Children in the University of Pennsylvania. Sixteenth edition, revised and enlarged. Pp. 1009; 149 engravings and 17 plates. Philadelphia and New York: Lea & Febiger, 1916.

A book which has stood before the medical public for twenty-six years, and which has now reached the sixteenth edition, is one which it hardly seems necessary even to attempt to review critically. The length of time that this book has been published is a very accurate index as to its original character, and the fact that it has reached its sixteenth edition shows that throughout the years of its life it has been constantly and accurately revised, and that whatsoever has appeared new in therapeutics has been placed in it. In this new edition Dr. Hare has continued the same splendid type of book that it has been heretofore. He has embodied in the text such changes in methods of treatment as have been described since the appearance of the last edition and such recent researches as have modified in part our conception of the physiological action of some drugs. There has also been incorporated in the present edition the official preparations of the *United States Pharmacopœia* and the *British Pharmacopœia*. The general method of arrangement and grouping of the drugs and of the methods of treatment other than drugs has been preserved.

The whole work is a splendid exhibition of therapeutics, as well as a demonstration of what one can do had he the knowledge, the experience, and the thoroughness that the author reveals in his text. J. H. M., Jr.

The Practitioner's Visiting List for 1917. Four styles: Weekly, Monthly, Perpetual, Sixty patient. Philadelphia and New York: Lea & Febiger.

The *Practitioner's Visiting List* for this year has recently been issued. Those who have learned to depend on this little book

know its value. Those who have never used it have failed to avail themselves of a most convenient and practical aid to business efficiency in the practice of medicine. The *Practitioner's Visiting List,* issued in four styles, affords an easy and complete system for keeping the daily records of any practice, regardless of its size. In addition to the ruled pages for daily calls, this little book contains a text portion which embodies the sort of information so frequently needed by every physician; as, for example, a diagnostic table of eruptive fevers; a list of incompatibles; instructions for the examination of urine; and much other interesting data. To here attest its usefulness seems almost superfluous in view of the fact that for thirty years the *Practitioner's Visiting List* has been widely employed with satisfaction. G. M. P.

MEDICAL CLINICS OF CHICAGO, November, 1916. Philadelphia and London: W. B. Saunders Company, 1916.

THE November issue of the *Clinics* is initiated by the demonstration of Dr. Walter Hamburger, of The Modern Medical Treatment of Ulcer of the Stomach and Duodenum. This is a very interesting article, particularly well illustrated. The author shows by an apparatus which he has devised that the pain and sensations which arise in the course of gastric ulcer are not caused by hyperacid condition of the gastric contents, but are due entirely to the increased gastric muscle tonus, hyperperistalsis, gastric muscle spasm, and increased intragastric tension. He introduces a permanent tube in the stomach which is attached to an inflated balloon, which in turn is so fixed that the movement of this balloon may be registered on a smoked drum. In this way he is able to verify clinically the researches of Dr. Carlson. A minor point which does not seem fair to the originator is the calling of the Einhorn tube a Rehfuss tube. The latter made a very moderate change in the shape of the capsule, but in no way modified the tube otherwise, so the credit of the innovation should belong to Einhorn.

The next two clinics are upon a very trite subject, poliomyelitis, and are very well presented by Drs. Abt and Hamill.

Dr. Mix then shows two cases of primary pernicious anemia. Dr. Mix's opinion that this type of anemia is infectious in origin and that the infection producing organism is the spirochete of syphilis does not seem to be backed-up by very adequate arguments. In fact the arguments that he employs could be similarly used to prove that the etiology of the disease is based upon entirely dissimilar causes.

Dr. Pusey then presents a skin case, which is followed by Dr.

Tice with two cases, one showing Addison's syndrome and the other gangrene of the lung.

Dr. Kretschmer discusses the treatment of chronic colon pyelitis by pelvic lavage. Dr. Kretschmer says that the present consensus of opinion is in favor of the lymphatic route for these infections. It seems, however, that it is the opinion of a very large number of genito-urinary surgeons that the hematogenous route is the one most generally described as the important cause of infection to the renal pelvis.

Dr. Williamson in the next sections discusses a patient with polycystic kidneys; another one with recurrent endocarditis; and a third patient with an atypical case of gout. Dr. Williamson says that gout cannot be differentiated from rheumatism in many cases. As a matter of fact, if the blood uric acid and the blood urea or blood non-protein nitrogen be estimated at the same time acute rheumatism usually can be differentiated very readily from acute gout and chronic cases of gout can be separated from chronic arthritis.

Dr. Smithies concludes this number of the *Clinics* with a very interesting and careful exposition of cardiospasm associated with diffuse dilatation of the esophagus and the treatment by means of dilatation bougies. J. H. M., Jr.

Applied Immunology. By B. A. Thomas, A.M., M.D., Professor of Genito-urinary Surgery in the Polyclinic Hospital and College for Graduates in Medicine, and R. H. Ivy, M.D., D.D.S., Assistant Instructor in Surgery, University of Pennsylvania. Second edition. Pp. 364; 68 illustrations. Philadelphia: J. B. Lippincott Company, 1916.

The second edition of this useful book will find ready welcome by those who wish to have well-balanced information concerning the basis and practical application of our knowledge of immunity. The authors have revised the first edition without greatly adding to its bulk, a highly praiseworthy achievement, for there is a tendency to add fresh material without condensing. The subject is put in a pleasant, readable style. Many references are given in the text, but it would enhance the book if more were added so that readers might seek extensive, authoritative articles. The illustrations have the merit of illustrating.

Drs. Thomas and Ivy present the application of immunology with due attention to its limitations, and, while showing what good may be done, point out that no one of our procedures is incapable of failure. They emphasize the need of studying cases from the stand-point of their immunity and of knowing exactly what the infection is and is doing. In this respect it seems to the reviewer that somewhat more space might be devoted to the protection of

persons getting foreign serums, such as dividing the dose, never giving a single dose of serum, but following the first by another, may be smaller one, to throw the patient into an anti-anaphylactic state, and the use of atropin. These things can all be done, and should be done, in persons who show allergie to plant protein, as pollensis, or to vegetable protein, as berry rashes, or to animal protein, as shell-fish.

While the authors justly denounce the use of phylacogens indiscriminately, this is a closely related subject of leukocytosis and bacterinization by non-specific proteins which is being used in certain forms of arthritis and to which some attention is due if only to point out the limitations. The attention of the authors should be called to the word "exoteric" on page 221, the meaning of which would be esoteric there. The error is in both editions; doubtless exotoxic is intended. H. F.

THE SEX COMPLEX. A STUDY OF THE RELATIONSHIP OF THE INTERNAL SECRETIONS TO THE FEMALE CHARACTERISTICS AND FUNCTIONS IN HEALTH AND DISEASE. By W. BLAIR BELL, B.S., M.D., London, Examiner in Gynecology and Obstetrics to the University of Belfast, and to the Royal College of Surgeons, England. Pp. 233; 50 illustrations. New York: William Wood & Co., 1916.

"PROPTER secretiones internas totas mulier est quod est."

Because of his belief and the importance of the subject to physiology and gynecology, the author has amplified and rewritten in book form, in the hope of stimulating interest and adducing new facts, his investigations and communications as first announced in the Arris and Gale Lectures in 1913, in which he first attempted to demonstrate that the reproductive functions are governed by all the organs of internal secretion acting conjointly, rather than by the gonads alone, as formerly thought.

The subject matter is divided into two parts. Part I deals with the morphological, physiological, and psychological considerations. Due consideration is given to the primary and secondary sex characteristics. He discusses the functions of the ovaries and the effects of oöphorectomy on the genitalia, general metabolism and the several ductless glands, also the relation of the thyroid, parathyroids, pineal, pituitary, thymus, suprarenals, pancreas, and mammary glands to the genital system, as deduced from extensive animal experimentation concerned with the removal of these endocritic organs. In other words the disquisition resolves itself into (1) a consideration of the factors which lead to the production and maintenance of the normal characteristics and functions of woman, so far as her feminine

attributes, primary and secondary, both of mind and body are concerned, and (2) a discussion of the morphological and physiological derangements of the sex complex. With the assumption "that femininity itself is dependent on all the internal secretions," the author by his experimental and histological studies, supported by fifty illustrations, almost all of which are photomicrographs of experimental ductless glands, concludes that the ovaries must be considered as part of a system, to which most, if not all, the other endocritic glands belong, and in which they, in their relation to reproduction, are as much concerned as the ovaries themselves, which by their hormones particularly, are able to bend the metabolism of the body to this purpose. Indeed, Bell would have us believe that the thyroid, pituitary, and suprarenals influence the development and subsequently preserve the integrity and activity of the genitalia, while the thymus and pineal prevent sexual precocity.

Part II is given over to pathological considerations, especially derangements in the structural and functional development of the genital organs and their functions, derangements of the fully established female characteristics and functions and sexual and reproductive psychosis and neuroses.

The classification of hermaphroditism and its consideration, together with puberty, is the most scientific, complete and best we have seen. All in all, this work of Bell is highly commendable and the book, most creditable from the publisher's stand-point, is a valuable addition to modern medicine, commanding the serious attention of all practitioners interested in gynecology and andrology.

B. A. T.

THE CRIMINAL IMBECILE. AN ANALYSIS OF THREE REMARKABLE MURDER CASES. By HENRY HERBERT GODDARD, M.D. Pp. 154. New York: The Macmillan Company.

THIS is a very interesting book on the criminal imbecile. It is an analysis of three rather well-known homicide cases in each of which the defendants were tried for murder. In the Gianini case the Binet-Simon tests were used perhaps for the first time in the history of legal medicine in this country. More remarkable still the jury acquitted the defendant on the ground of criminal imbecility. In the Roland Pennington case the jury found the man guilty and he was only recently electrocuted. This case was especially interesting to Philadelphians, inasmuch as the crime was committee only a few miles from this centre. In both of these cases the author acted as an expert. The third case is equally interesting but the author did not have the opportunity to study him.

The whole point of discussion is that in all of these cases the defendants were high-grade imbeciles and emphasis is laid on

the fact that in so many similar instances this is the case. This problem will never be solved as long as this type of individual is allowed at large. In the experience of the reviewer as well as the experience of all alienists it is common to run across such individuals and the problem is what to do with them. Not long ago with other physicians the reviewer examined many individuals in the Philadelphia House of Correction in which many such imbeciles were found. Yet there is no law which allows the city to hold these individuals and to treat them. As a consequence the reviewer made an inquiry as to whether there were laws which gave courts the right to examine these individuals for the purpose of placing them in institutions which could control them. In only one instance did he find that there was such a law. Nothing can ever be accomplished until the National Government takes up this matter and makes it possible that throughout the whole United States similar measures should be adopted. So long as each city or State is allowed to make its own laws or rather do without any law, just so long the question of the criminal imbecile will be a standing menace to the community. T. H. W.

AN INTRODUCTION TO THE STUDY OF COLOR VISION. By J. HERBERT PARSONS, D.Sc., F.R.C.S. Cambridge University Press, New York: G. P. Putnam's Sons.

WITH this study of color vision the author has given us another volume that maintains the high standards attained by his previous works. The vast literature on this subject has been reviewed, sifted, and woven together in a work that presents the important facts concerning the subject in a manner that will make this volume of real use to those interested in this subject. There are but few men, confining their energies to ophthalmology, who are as well qualified as the author to write a volume of this character, for aside from his qualification as a practitioner and pathologist he has shown much interest in vision in its various phases and has made a number of valuable contributions to this subject.

The work is divided into three parts: The first discusses the chief facts of normal color vision; the second, the chief facts of color blindness; the third, the chief theories of color vision. The first two parts are of greater interest to the physiologist and psychologist, but they contain much that the practical ophthalmologist could absorb with profit, but it will require careful and thoughtful reading, owing to the mathematical and experimental character of the work. Part three deals with the more practical side of the subject, and in it are discussed the Young-Helmholtz and Hering

theories as well as the theories of Donders, Ladd-Franklin, McDougall, Schenck, Wundt, Müller, and Edridge-Green.

In the reviewer's experience there is probably no branch of ophthalmology concerning which the average practitioner has such a limited knowledge. In this volume this intricate subject is handled in the masterly way one would expect when we consider both the scientific and practical training of the author. T. B. H.

Refraction of the Human Eye and Methods of Estimating the Refraction. By James Thorington, A.M., M.D. Pp. 407; 347 illustrations, 27 in colors. Philadelphia: P. Blakiston's Son & Co.

In order to simplify the work of the student, the author has very wisely condensed his volumes on *Refraction and How to Refract*, *Prisms*, and *Retinoscopy* into one volume. In so doing he has produced his best work, and one that is certain to meet with popular approval. The volume is divided into twenty-three chapters, so arranged that beginning with optics the student is judiciously and easily lead through the various phases of the subject until the more practical part, dealing with refraction, is discussed, and finally the measuring and fitting of glasses. The generosity with which the volume is illustrated also adds much to the convenience of the reader.

The author is not only to be congratulated on the appearance of his most satisfactory work, but also in his decision to eliminate certain obsolete test from a practical manual of this type.

T. B. H.

Diseases of the Skin. By Richard L. Sutton, M.D., Professor of Diseases of the Skin, University of Kansas School of Medicine; Dermatologist to the Christian Church Hospital. Pp. 916; 693 illustrations and 18 colored plates. St. Louis: C. V. Mosby Company, 1916.

Sutton's text-book on skin diseases is a variant from the modern large treatises published in this country on cutaneous affections: (1) it contains from 100 to 400 pages less; (2) fully twice as many illustrations are employed as in any other book, exclusive of an atlas; (3) more stress has been laid upon the pathology, and there are more illustrations depicting the histopathology of this subject than in all of the other American cutaneous treatises combined.

Naturally with the lessened text and the doubled space occupied by the illustrations the detailed description is not so complete as in

the other large treatises. A considerable amount of repetition has been avoided, which naturally saves quite a few pages.

Sutton uses the classification as originally adopted by Hebra and modified by Crocker, and therefore sticks to the conservative rather than attempting a more modern but possibly too extreme adaptation of the etiological factors. The preliminary chapters on general etiology, pathology, and diagnosis are concise, and contain the modern views upon the subject. The massive dose method of roentgen therapy and radium treatment are ably described in addition to all of the other therapeutic measures. The volume contains all of the newer diseases, such as cutaneous thrush, foot-and-mouth disease, trichinosis, etc.

The writer is particularly fortunate in being located in the West, and therefore having had unusual opportunities in observing and treating blastomycosis and sporotrichosis. Friends of the author have supplied excellent photographs of cutaneous outbreaks in the American Indian, the negro from our Island possessions, and elsewhere. The peruser, therefore, has the opportunity of studying practical illustrations of frambesia, espudia, gangosa, erythrasma, Norwegian scabies, tinea imbricata, etc. Several color plates illustrate beautifully foot-and-mouth disease, angiokeratoma, the histopathology of nevus linearis, hemorrhagic sarcoma of Kaposi, lupus erythematosus, and ulcerating granuloma of the pudenda.

The section on carcinoma is particularly good, and divides the subject into the squamous-cell and the basal-cell, depending upon the portion of the skin from which the growth takes its origin. Treatment for this prevalent disease is fully described. Syphilis is given in detail, and the section on the therapeutic measures is lucidly and valuably written. The various exanthemata are exploited under the heading of Inflammations. The illustrations depicting the mucous membrane and nail diseases are unusually clear and therefore of enhanced value.

Sufficient references are cited to give those who care for extensive research a survey of the more valuable literature.

If criticism were to be offered, the suggestion might be made that too many photographs are employed under certain diseases depicting the same characteristics; that some of the illustrations of different cutaneous outbreaks are absolutely indistinguishable the one from the other, such as those picturing psoriasis of the palm, seborrhoic eczema and squamous eczema of the same location. A score or more of the photographs should be discarded because of lack of distinctness of detail; this fault it is only fair to state is probably due to the publisher rather than the author.

The volume is attractive in every detail, well-printed, and the paper is sufficiently highly glazed to give a clearness and practical detail to most of the illustrations. The author is to be congratulated upon the excellence of his work and the valuable addition he has made to American dermatology. F. C. K.

WHO IS INSANE? By STEPHEN SMITH, M.D. Pp. 285. New York: The Macmillan Company, 1916.

THIS is an extremely entertaining book. The author in 1882 was appointed State Commissioner in Lunacy, occupying this position for about six years. On assuming office Governor Cornell informed him that there was a popular belief that many asylum inmates were not insane and advised him to keep constantly in mind in visiting the asylum the question, "Who is Insane?" The author apparently accomplished a great deal, for during his service he effected: (1) the introduction of the Training School for Attendants; (2) the creation of a State Commission in Lunacy; (3) the removal of the insane from County to State care. No State in the union takes better care of its insane than New York. Some of the other States, notably Massachusetts, has followed in its footsteps. The reviewer with other neurologists has tried to get the Pennsylvania legislature to adopt the methods of New York and it is the hope of Pennsylvania physicians that such methods will some day be adopted. This is only mentioned to show what the author of this work has apparently helped to accomplish.

The book is meant for the layman. He first discusses "who is insane" and "what is insanity" and gives some very interesting and dramatic stories to illustrate his points. Later on he discusses the critical periods of life predisposing to insanity, care and treatment of the insane, the lessons applied to the feeble-minded and criminal, and lastly he indulges in the hope that some day better things can be accomplished. For the layman it is an excellent introduction into insanity and what it means, for the author has had the good judgment to not only make his work instructive, but sufficiently interesting so that anyone will be bound to finish the book.

T. H. W.

SURGICAL AND GYNECOLOGICAL NURSING. By EDWARD MASON PARKER, Surgeon to Providence Hospital, and SCOTT DUDLEY BRECKENRIDGE, Gynecologist to Providence Hospital, Washington, D. C. Pp. 402; 134 illustrations. Philadelphia and London: J. B. Lippincott Company, 1916.

THIS work takes up in a very thorough manner, from both a theoretical and practical stand-point, the essentials of nursing as applied to surgical and gynecological work. Opening with a brief consideration of the cell as the body unit, it goes on to explain the nature and modes of infection, with a *résumé* of the most important points of surgical pathology. The remainder of the book is eminently practical. The succeeding chapters explain in considerable detail the various measures of what may be termed "minor nursing,"

such as postures, bandaging, the giving of enemas, hypodermics, enteroclysis, etc., with useful sections on methods of obtaining fractional doses from hypodermic tablets of standard strength and comparative tables of the metric and English systems. The actual work of the operating room is then discussed, with very practical lists and group illustrations of the instruments needed for all the ordinary major operations. The routine nursing of operative cases is admirably discussed, with a brief chapter on the most important postoperative complications for which the nurse should be on the watch. The work, as a whole, is refreshingly sane and practical; it has obviously been written by men who are in daily contact with the problems presented, and there is no evidence of "padding," in the way of unnecessary refinements or complications which look well on paper, but are always discarded in actual work. Thus, when the fullest aseptic precautions are not required in certain procedures, this fact is frankly stated. The general excellence of the work, as a whole, is so marked, however, that one rather glaring omission cannot be passed over in silence. In view of the almost universal employment today of dry sterilized gloves in the operating room, it seems strange that no good method of their preparation is described, the statement that "when the dry method is used, the gloves *after coming from the sterilizer* must be thoroughly dried between sterile towels, and then turned inside out and dried again; all this must be done by a 'clean' nurse wearing sterile gloves," being quoted only to be heartily condemned. The book, as a whole, is perhaps a trifle lengthy, but can be thoroughly recommended to those who want an excellent manual of all phases of surgical and operating-room nursing. G. W. O.

PHYSICS AND CHEMISTRY FOR NURSES. By AMY ELIZABETH POPE, Instructor in the School of Nursing, St. Luke's Hospital, San Francisco, Cal. Pp. 426; 74 illustrations. New York and London: G. P. Putnam's Sons, 1916.

THE book has for its purpose the presentation of such physical and chemical knowledge as every nurse should possess. It explains important chemical and physical processes and their relation to disinfection, cleaning, cooking, digestion, water supply, textiles, food adulteration, and metabolism. The subject matter is presented in a clear, simple, and concise manner, which makes it easily read. A great many experiments are described, "any or all of which," as the author states, "can be omitted without interfering with the value of the lessons." However, it is distinctly advantageous to include as many experiments as possible, since actual work in the laboratory is of such great value in acquiring a better understanding of the subject studied. H. D.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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The Lipoids ("Fat") of the Blood in Diabetes.—W. R. Bloor (*Jour. Biol. Chem.*, 1916, xxvi, 417), with the coöperation of E. P. Joslin and A. A. Hornor, has examined the blood lipoids in a series of cases of diabetes mellitus. The work is summarized as follows: In severe diabetes the blood lipoids were all markedly increased up to 100 per cent. or more of the normal values. In mild diabetes the lipoids may be normal. In general, the more severe or long standing the diabetic condition the more marked was the abnormality in the blood lipoids. In spite of the high values, the relations between the lipoids were practically those of normal individuals, indicating that the fat metabolism was essentially normal. There was a tendency, however, for the fat to accumulate in excess of the other constituents, and this fact and possibly also the high lipoid values foreshadow the lipemia. The high lipoid values noted occurred entirely in the plasma, the composition of the corpuscles remaining practically normal. The fact that cholesterol increased parallel with the fat in diabetic blood, even in severe lipemia, gives further support to the earlier assumption that cholesterol has a part, and probably an important part, in fat metabolism. For the same reason the determination of cholesterol in the plasma (a relatively simple process) should give valuable information regarding the lipoid content of the blood in diabetes. In the present series no definite relation could be found between high blood lipoids and the occurrence of acetone bodies in the urine. *Lipemia:* Lipemia was observed in but 2 of the 36 cases in this series and these were not

under treatment but were on an unrestricted diet. No lipemia was found in any of the cases under treatment. Evidence is presented to indicate that diabetic lipemia originates mainly in the fat of the food, and that the probable reason for its appearance in the blood is a partial failure of the mechanism for dealing with fat. Cholesterol increased parallel with the fat up to eight times its normal value, while lecithin is relatively little increased. Since lecithin formation has been found to be an early stage in the metabolism of fat, it is possible that the inability to form lecithin may be a factor in the production of the lipemia.

The Production of Amyloid Disease and Chronic Nephritis in Rabbits by Repeated Intravenous Injections of Living Colon Bacilli.—C. H. Bailey (*Jour. Exper. Med.*, 1916, xxiii, 773) finds that the repeated intravenous injection of rabbits with living Bacillus coli communis over long periods has resulted in the formation of amyloid deposits in the spleen, liver, and kidneys. Suppurative lesions were not present in most cases, and therefore not a factor in its production. The results have been constant in that amyloid was found in all rabbits, 8 in number, which were injected over a period of eighty-eight days or more. Eight rabbits showed amyloid in the spleen, 6 of these in the kidneys also, and 3 in the liver. The kidneys of these 8 rabbits also showed as a result of the injection a subacute and chronic glomerulitis, parenchymatous degeneration, some interstitial infiltration with round cells, and a slight cellular proliferation of connective tissue, thus resembling the chronic parenchymatous nephritis of man, which is so commonly associated with amyloid disease.

Chemical Versus Serum Treatment of Epidemic Meningitis.—S. Flexner and H. L. Amoss (*Jour. Exper. Med.*, 1916, xxiii, 683) have made an experimental investigation of the protargol treatment of epidemic meningitis recently proposed by Wolff, who had 5 recoveries out of 8 cases. While Wolff admits that the number of cases is too small to justify claims for a cure, yet he believes that the protargol treatment is at least harmless. The authors find that protargol is without beneficial influence upon experimental infections in young guinea-pigs and monkeys. On the contrary, they find that protargol exerts antileukotactic and antiphagocytic effects, and is also a potent protoplasmic poison. The leukocytes with which it comes in contact are injured and made to degenerate. According to the extent to which these harmful properties are excited, protargol promotes the advance rather than the restraint of the progress of meningococcic infection. Results analogous to those with protargol were obtained with lysol. The authors conclude that specific antiserum should be employed in the treatment of epidemic meningitis.

The Non-coagulable Nitrogen of the Blood in Intestinal Obstruction.—J. V. Cooke, F. H. Rodenbaugh and G. H. Whipple (*Jour. Exper. Med.*, 1916, xxiii, 717) report a study of intestinal obstruction, largely experimental, which they summarize as follows: Intestinal obstruction, as a rule, is associated with an increasing amount of non-coagulable nitrogen in the blood. With acute intoxication the rise in non-coagu-

lable nitrogen may be rapid, and reach as high as three or even ten times normal. With more chronic intoxication there may be little or no rise in the blood non-coagulable nitrogen. Closed intestinal loops show exactly the same picture, and when combined with obstruction may give very high nitrogen readings. Acute proteose intoxication due to injection of a pure proteose will show a prompt rise in blood non-coagulable nitrogen, even an increase of 100 per cent. within three or four hours. These intoxications also show a high blood content of creatinin and urea. The residual or undetermined nitrogen may be very high. A human case of intestinal obstruction with autopsy presents blood findings exactly similar to those observed in many animal experiments. Clinically, the non-coagulable nitrogen of the blood may give information of value in intestinal obstruction. A high reading means a grave intoxication, but a low reading may be observed in some fatal cases, and gives no assurance that a fatal intoxication may not supervene. The kidneys in practically all these experiments are normal in all respects. It is possible that protein or tissue destruction rather than impaired eliminative function is responsible for the rise in non-coagulable nitrogen of the blood in these acute intoxications. Transfusions of dextrose solutions often benefit intestinal obstructions and may depress the level of the non-coagulable nitrogen in the blood. Some cases show no change in non-coagulable nitrogen following transfusions and diuresis, and, as a rule, such cases present the most severe intoxication.

The Development of Malaria Parasites in Three American Species of Anopheles.—W. V. King (*Jour. Exper. Med.*, 1916, xxiii, 703) reports a study of the susceptibility to malarial infection of the three most prevalent species of anopheles in this country. He has found that Anopheles punctipennis is an efficient host of the organisms of tertian and estivo-autumnal malaria and Anopheles crucians may likewise transmit the estivo-autumnal parasites. Anopheles quadrimaculatus has been known to be an efficient host since Thayer's experiments in 1900. With Anopheles punctipennis, developmental forms of the sporogenic cycle of Plasmodium vivax were demonstrated in 6 of 7 mosquitoes dissected and of Plasmodium falciparum in 4 of 20 specimens. With Anopheles crucians, oöcysts or sporozoites, or both, of Plasmodium falciparum were found in 9 of 12 specimens dissected. No tests were made with this species and Plasmodium vivax. Anopheles quadrimaculatus was employed as a control species in the experiment and became infected, as in the following ratio: 8 of 12 specimens with Plasmodium vivax and 3 of 19 specimens with Plasmodium falciparum. The number of observations is comparatively small, but it would seem that Anopheles punctipennis and Anopheles quadrimaculatus are equally susceptible to infection with Plasmodium vivax. With Plasmodium falciparum, Anopheles crucians showed the highest percentage of infection, with Anopheles punctipennus second, and Anopheles punctipennis third.

SURGERY

UNDER THE CHARGE OF

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Transplantation of Fascia for Pointed-toe Deformity.—Orth (*Zentralbl. f. Chir.*, 1916, xliii, 812) says that pointed-toe deformity has increased of late in military and non-military service. In many cases gymnastic and other corrective exercises were unsuccessful, and only operation gave hope of making the patients useful. So long as the tendons are not too much contracted or degenerated by cicatricial tissue, the methods of Beyer and Vulpius are sufficient. But when these conditions do exist or the original lesion affects the tendon itself, we may lengthen the tendon by the transplantation of a suitable piece of fascia to fill the gap resulting from the division of the tendon. The transplanted piece of fascia did not become necrotic or contract. Passive movements were begun after fourteen days and active movements after three to four weeks. The results were good in three soldiers so operated on. Two of them returned to service in the field and one to garrison duty.

Proving the Collateral Circulation in a Case of Femoral Aneurysm by the Henle-Coenen Sign.—Dreyer (*Zentralbl. f. Chir.*, 1916, xliii, 825) proceeded as follows in a case of aneurysm in Hunter's canal: He exposed the femoral vessels central to the aneurysm in an easily accessible place and clamped the artery here. He then isolated the vessels in the popliteal space, and divided a lateral branch of the popliteal artery. The free bleeding from the central end of the divided branch proved a sufficient collateral circulation to justify the application of a simple ligature to the femoral artery on the central side and another to the popliteal artery on the peripheral side of the aneurysm. There was not the slightest disturbance in nutrition. The patient got out of bed on the eighth day and walked around. The author offers the following modification of the proof of the condition of the collateral circulation: The application of a preliminary clamp on the peripheral as well as on the central side of the aneurysm.

The Electromagnet in War Surgery.—Cords (*Zentralbl. f. Chir.*, 1916, xliii, 865) refers to Capelle's article on the treatment of erysipelas with artificial sunlight and relates his own experience with the method. He begins with daily ten-minute exposures and obtains favorable results. Recently he began to use exposures to the rays of the sun. According to his small experience, the exposure to the free air and sun is to be preferred to the exposure to artificial sunlight. One patient with recurring erysipelas and a perforating, sequestrating, gunshot

wound of the thigh, had become exhausted from several attacks of erysipelas and long-continued fever. In the midst of the fever, he was left continuously on a veranda, with the naked limb exposed to the air and sun. In two days the temperature had fallen to normal and the erysipelas had disappeared. He recovered rapidly but after a longer interval than usual had a recurrence of the erysipelas. This attack, however, was of much shorter duration than the preceding ones, which were much more severe.

The Effect of the Pointed Bullet on the Shaft and Ends of the Bone.—Mackowski (*Deutsch. Ztschr. f. Chir.*, 1916, cxxxvii, 403) says that extensive splintering was found most frequently in the shaft and usually in what is termed the butterfly figure. This resulted when the bullet struck about midway in the width and length of the bone. When it struck the shaft in the middle of its width and near the epiphyseal end, the fragments lying toward the middle of the shaft were longer than toward the epiphyseal end, which often broke off transversely. When the bullet so hit the shaft as to divide it into two unequal parts, the larger fragment broke into large fragments and the smaller into smaller fragments. The stronger and thicker the shaft, the larger were the fragments. In fractures of the shaft of the femur the fragments were larger than in fractures of the shafts of the smaller bones, as the forearm and leg. Fractures of the shaft without division of continuity occurred almost always in the slender forearm and leg bones. They were not observed in the humerus or femur. The most frequent fracture of the femoral shaft is the large splintered oblique fracture with long pointed fracture ends. Transverse fractures were seen almost only in the shaft of the humerus. The humeral head was usually bored through without splintering, although in some cases small splinters occurred.

Gunshot Wounds of Peripheral Nerves.—Stookly (*Surg., Gynec. and Obst.*, 1916, xxiii, 639) based his paper on a study of 75 cases of nerve injuries, observed in the present war in the British Military Service. He says that peripheral nerves may be injured by projectiles, pieces of bone or foreign bodies, and may be implicated secondarily by scar tissue, or callus, or both. Diagnosis cannot be made before operation between anatomical and physiological division. Diagnosis can usually be made in cases with incomplete division. In war surgery primary suture is rarely possible due to infection. Operation is indicated when complete division is diagnosed. Nerve freeing is in many cases to be preferred to excision and suture. When the nerve is widely implicated and there is a large loss of continuity, it is better to do nerve transference or nerve transplantation than tubulization or suture with the nerve under tension. Stretching of the nerve should not be done as it causes karyolysis of the nerve cells in the anterior horn with subsequent degeneration of the nerve axon in the proximal nerve trunk. Efficient splinting to prevent contractures and overstretching of the muscles is imperative, both before and after operation. The musculospiral nerve injured in its lower third does show loss of sensation on a narrow band over dorsum of thumb, usually only loss to cotton-wool and temperature sense. Injury to the musculospiral

may cause dissociation of temperature sense in the area on the dorsum of the hand—without loss to cotton-wool. Return of motor function begins with the muscles which first receive their supply below the lesion. The return is earlier the nearer the lesion to the periphery. Trophic ulcers occur only after trauma. Their repair appears to be no different than in other parts.

A Study of Exstrophy of the Bladder.—Stevens (*Surg., Gynec. and Obst.*, 1916, xxiii, 702) presents a study of the literature and reports a case five years after implantation of the ureters into the rectum. He reported the patient at work, in perfect health, and changed from a wretched, dejected, lonely boy to a bright and happy lad with a real interest in life. Stevens emphasizes the wisdom of a careful preliminary examination of the kidneys before any operation is undertaken on a case of exstrophy of the bladder. The operation is clearly indicated if there be no severe renal infection. Methods which effect no control of the urine offer but little comfort to the patient. The simpler procedures that do provide a sphincter are to be preferred. The newer methods which form an extra-intestinal, perineal channel, lined with epithelium and controlled by the sphincter ani, have not been sufficiently tested clinically. The author believes that uretero-intestinal anastomoses offer the exstrophy patients the best outlook at the present time. The subject is intimately associated with bladder exclusion for other ailments, and the problem of control of ascending infection is deserving of all the experimental and clinical work being done. Bergenheim's operation is the best for this condition. It consists essentially of the independent extraperitoneal implantation of the ureters, each with a rosette of bladder-wall, into the rectum, with removal of the bladder. Preservation of the ureteral sphincter is worth while, whether it acts as a valve or sphincter or whether its preservation merely offers a more circuitous and less likely route for ascending infection to follow in order to reach the ureteral lymphatics.

Direct Neurotization of Paralyzed Muscles.—Steindler (*Am. Jour. Orthop. Surg.*, 1916, xiv, 707) studied experimentally on dogs the Heineke idea of the possibility of implanting peripheral nerves directy into paralyzed muscles. Heineke maintained that motor impulses can in this way be directly transmitted to the muscle. A further step was taken by Erlacher in maintaining the possibility of neutralizing the paralyzed muscles by means of direct contact between normal and paralyzed muscle, and without the implantation of the peripheral nerve. The author found that direct neurotization, in the sense of Heineke and Erlacher, is indeed possible. The natural limits of physiological regeneration allows motor nerve, directly implanted into paralyzed muscle tissue, to establish by regeneration the entire chain of neurometer connections. From the experiments it appears that this regeneration becomes complete in from eight to ten weeks after the implantation. In close succession to the regeneration of nerve tissue the muscle tissue also regenerates, and this becomes manifest in the reappearance of the normal contours of the fibers and the normal striations. Physiological test of the reneurotized muscles also show that regeneration of the muscle takes place centrifugally from the

point of implantation. In none of the experiments was there observed in a normal muscle any inclination to take on additional nerve supply, though ample occasion was furnished for this effect. For this reason Steindler is inclined to be rather skeptical about the question of hyperneurotization. Apparently totally paralyzed muscles in infantile paralysis were regularly found to contain a variable number of perfectly normal muscle fibers and a considerable amount of nervous elements. A definite statement concerning the clinical application of these facts to cases of infantile and other paralysis should be withheld until one or two more points are more clearly understood.

THERAPEUTICS

UNDER THE CHARGE OF

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The Treatment of Syphilis of the Central Nervous System.—WALKER and HALLER (*Arch. Int. Med.*, 1916, xviii, 376) report 75 patients with central nervous system syphilis treated with 450 intraspinal injections of salvarsanized serum and with 350 intravenous injections of salvarsan. At first only salvarsan intravenously was used, and a few patients improved rapidly. However, in many cases little or no improvement followed from three to six injections, so these patients were then given intraspinal salvarsanized serum in conjunction with the salvarsan, and they improved rapidly under the combined treatment (Swift-Ellis method). As the intraspinal treatment seemed to reinforce the salvarsan the authors desired to determine what results would follow the intraspinal method alone. For this method they selected patients with a negative Wassermann reaction in the serum and with positive findings in the spinal fluid. The results from this method closely paralleled those from the double method. Therefore, the following rule has been adopted at the Peter Bent Brigham Hospital: Patients are first treated with intravenous salvarsan. If satisfactory results do not follow three or four such treatments, they are then given intraspinal salvarsanized serum in conjunction with intravenous salvarsan. Those who have a negative reaction in the serum are given only intraspinal salvarsanized serum. To thirteen patients were given five or more intravenous injections of salvarsan alone. Four of these patients, three with cerebrospinal syphilis and one with syphilitic meningitis, had very recent infections and were relieved of their symptoms. The spinal fluid cell count was reduced to normal in three cases, and the Wassermann reaction became negative with 1 c.c. in three cases. The remaining nine patients had older infections and they showed little or no improvement in their symptoms and no improve-

ment in the spinal fluid findings. To thirty patients were given three or more double (Swift-Ellis) treatments, and marked improvement followed in each case. Thirteen patients who were previously incapacitated were restored to working capacity; of eighteen with ataxia, eight were relieved, five were markedly improved and five more were much improved. Seventy-five patients showed improvement in the spinal fluid Wassermann reaction; in ten cases this amounted to from 0.3 c.c. to 0.5 c.c., and in five other cases the reaction became negative with 1 c.c. The spinal fluid cell count became five or less in twenty-five cases. In four cases a period of two years has elapsed since treatment without any return of symptoms, in three others a period of eighteen months and in eight others six months or more. Four patients have shown some form of relapse. One with tabes had a relapse in ataxia, two with general paresis of the insane had a temporary relapse in mentality, while one with cerebrospinal syphilis developed a weakness in the legs probably of cerebral origin. Seventeen patients were treated intraspinally with salvarsanized serum alone, and all were markedly improved or relieved symptomatically. Nine who were previously unable to work were restored to working capacity. Of the seven patients with ataxia, four previously unable to work at all, became able to work, and in the other three, in whom the ataxia was not so marked there was great improvement. The Wassermann reaction in the spinal fluid became negative with 1 c.c. or 2 c.c. in eight cases, and in five others it was improved from 0.3 c.c. to 0.5 c.c. The spinal fluid cell count became normal in nearly every case. Two patients with syphilitic meningitis were relieved in every way. Seven patients have been observed twelve months since treatment was stopped, and four others for six months or more, and they show no return of symptoms. One patient with cerebrospinal syphilis had a return of headache after eight months, and two with tabes had a slight relapse in ataxia, which rapidly cleared up immediately following a treatment. In one patient a provocative Wassermann reaction occurred in the spinal fluid following the administration of salvarsan and in two cases a provocative reaction occurred in the spinal fluid following intraspinal treatment. Two patients with repeatedly negative reactions in the serum while under intraspinal treatment developed a positive reaction in the serum about the time the spinal fluid reaction became negative with 1 c.c. Improvement in symptoms following treatment seemed to parallel fairly closely the drop in the cell count, and those patients with high cell count seemed to improve symptomatically more rapidly and the cell count dropped more rapidly than occurred in those cases with low cell count. The only physical sign which was changed in these cases was that a positive Romberg in one case became negative. More benefit seemed to follow moderate after-treatment reactions than when no reaction occurred. Severe reactions are undesirable and may be avoided by less frequent treatments. In this series of cases no fatal or disturbing results followed treatment. In this series of cases the total number of cells in the spinal fluid did not vary as a rule. In a few cases of tabes, during severe crises of pain, and in cases immediately following too frequent and too large intraspinal injections of salvarsanized serum, the cell count temporarily increased. In their conclusions the authors state that patients with recent syphilitic meningitis and cerebrospinal

syphilis may be relieved symptomatically by intravenous salvarsan; the spinal fluid Wassermann reaction may become negative with 1 c.c. and the cell count may become normal. Patients with long-standing cerebrospinal syphilis and tabes may be benefited symptomatically following salvarsan intravenously, but little or no change occurs in the spinal fluid findings. Patients with recent and those with late syphilitic meningitis, cerebrospinal syphilis, tabes and general paresis of the insane are markedly improved following the combination of intravenous salvarsan and intraspinal salvarsanized serum (Swift-Ellis method), and those who fail to improve under salvarsan alone do improve both in symptoms and in spinal fluid findings following this double treatment. That intraspinal salvarsanized serum greatly benefits patients with central nervous system syphilis is shown by the fact that those with negative serum reactions and with positive spinal fluid findings are symptomatically relieved by this treatment. In many patients the spinal fluid Wassermann reaction becomes negative with 1 c.c., the cell count becomes normal and a negative (Noguchi) globulin test is obtained following sufficient treatment with salvarsanized serum intraspinally without other medication.

Antidotes in Mercuric Chloride Poisoning.—Fautus (*Jour. Lab. and Clin. Med.*, 1916, i, 879) from an experimental study concludes that egg albumen is of little value as an antidote to mercuric chloride, unless it is given immediately after the poison is swallowed. Milk and serum albumen are worthless. Hall's solution (potassium iodide and quinin) is useless as an antidote. Sodium bicarbonate and sodium acetate possibly have a moderate antidotal value. Sodium carbonate is of no value. Potassium bitartrate and sodium sulphate have no antidotal value. Stannous chloride has little antidotal value. Calcium sulphite is probably too toxic to be of use as an antidote. Sodium phosphite alone has no antidotal value, but mixed in a certain proportion with sodium acetate it has antidotal efficiency. Sodium hypophosphite mixed with a certain proportion of sodium acetate or of hydrogen peroxide is also highly efficacious as an antidote. As the result of his studies, Fautus recommends the following antidotal treatment for mercuric chloride poisoning: Immediate administration of a tablet composed of sodium phosphite, 0.36 gm., and sodium acetate, 0.24 gm. If this be not available, give the following: Sodium hypophosphite, 1.00 gm., water 10.00 c.c. and hydrogen peroxide, 5.00 c.c. If the amount of the poison taken be known, ten times as much of the hypophosphite should be given as poison was taken. As this might require a large and possibly harmful amount of hypophosphite, it should immediately be followed by copious lavage, with a very dilute solution of the antidote. This may be followed by a safe dose of the antidote, which is to be retained, and which might be repeated every eight hours for several days. This antidotal treatment might be combined with some such eliminant treatment as recommended by Lambert and Patterson.

The Ultimate Results in the Treatment by Artificial Pneumothorax.—Shoetle (*Jour. Am. Med. Assn.*, 1916, lxvii, 1268) reports 104 cases of pulmonary tuberculosis treated by artificial pneumothorax. The

first of this series of cases began treatment in May, 1912, the last in August, 1914. Seventy-five of these cases are to be eliminated as they proved inoperable, and are of interest only in showing that almost one case out of four had such extensive adhesion that operation was impossible. This leaves 79 cases that allowed of sufficient collapse to produce therapeutic effects. Of the seventy-nine patients, thirty-five are dead, two were apparently made worse; eighteen were improved, and twenty-one were discharged and treatment stopped as being symptomatically cured. Twelve of the eighteen marked "improved" are still under treatment. Of the twenty-one patients discharged as symptom fell, nineteen were third stage, two were second stage cases, seventeen were progressive and four were stationary. Sputum was positive in all. All were febrile cases and all had tried the usual rest cure and climate treatment. The majority were sanatorium cases and all had failed. These patients have now been without pneumothorax treatment for the following periods: two over three years; four over two years; five over one and one-half years; six over one year, and four for six months or over. Two have relapsed and died. Of the remaining nineteen, fifteen are well and working, and three others were when last the author heard of them; one is now ready for employment. Shoetle believes that the treatment is best carried out in an institution where proper after-care can be given. He also advises small injections of gas, never exceeding 500 c.c., and as a rule from 250 to 350 c.c.

Exophthalmic Goitre.—Ochsner (*Ann. Surg.*, 1916, lxiv, 385) in speaking of the treatment of exophthalmic goitre following operation states that with the exception of a very small number of cases in which an insufficient amount of the gland had been primarily removed, or in which the remnant which had been left at the primary operation had increased in size, and which have had a recurrence of symptoms, he has almost invariably found that they had either disregarded the directions given regarding diet and rest and hygiene or they had been permitted to return to their homes without definite instructions in this direction. He believes that it is very important that written or printed directions be given these patients and that they be thoroughly impressed with the importance of following these directions. The rules as formulated by Ochsner are as follows: Avoid all excitement or irritation of every description. An abundance of rest is important, and should be obtained by going to bed early and taking a nap after luncheon. Have an abundance of fresh air at night. Eat and drink nothing that irritates the nervous system such as tea, coffee, or alcohol. Do not use tobacco. Eat very little meat. If very fond of meat, take a little beef, mutton or breast of chicken or fresh fish once or twice a week or at least three times a week. Drink a great deal of milk and eat food prepared with milk such as milk toast, milk soups, etc. Cream and buttermilk are especially good. Avoid any kind of meat broths. Eat an abundance of fresh fruit and cooked vegetables, or very ripe raw fruits, or drink fruit juices prepared from ripe fruit. Eat plenty of eggs, bread, butter, toast, rice and cereals. Drink an abundance of good drinking water, or if this is not available, boil the drinking water or drink distilled water.

OBSTETRICS

UNDER THE CHARGE OF

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Puerperal Gangrene of the Extremities.—STEIN (*Surg., Gynec. and Obst.*, October, 1916) contributes an interesting paper upon this subject in which he cites reported cases and contributes two. His first case was that of a woman, aged twenty years, in apparently good general health. She was about three months pregnant. The pelvic organs were apparently normal, and it was suspected that the patient had become infected. Shortly after admission to the hospital a three months' abortion occurred with foul odor from the fetus and from the vagina. The next day the temperature became normal, but in the evening rose to 105° F. During the next six days the patient's temperature varied from 104° to 105° without pain and other symptoms. On the seventh day examination showed numerous grayish-white superficial ulcers around the cervix covered with whitish membrane. Some placental tissue was removed by a curette and the interior of the uterus was swabbed with tincture of iodin. This was repeated for the next seven days. The temperature remained between 101° and 102° F. Seven days after the curetting the patient complained of pain in the right leg and three days later the right leg and foot became cold and swollen with bluish discoloration. The foot was extremely painful to touch and the pulsation of the dorsalis pedis artery could not be felt. The whole foot became gangrenous. A line of demarcation formed and amputation had to be done below the knee. The heart remained normal. Several blood cultures showed no growth. The Wassermann test was negative. On examining the amputated tissue there was no thrombus in the anterior tibial or the dorsal artery of the foot. At the termination of the perineal artery there was a thrombus in the necrotic muscle and there were thrombi in the veins. In the literature this is the fourth case on record in which gangrene has followed abortion. In all of the other cases there was a vegetative endocarditis. The second case was one of labor at full term in a primipara, aged nineteen years, who was in good general condition. The Wassermann reaction was negative. Delivery was effected by a median application of the forceps and laceration repaired with chromic catgut suture. Two days afterward there was a slight chill with temperature of 104.5° F. There were ulcerations around the cervix and in the urine were found albumin and hyaline casts. The lacerated area sloughed and the tissues were removed. The patient's fever continued although the heart remained in good condition. Twelve days after confinement the patient insisted on leaving the hospital. She returned seven days later or nineteen days after confinement with a rigid abdomen, temperature 102° to 104° F., and pulse 110. Both feet were gangrenous about four inches above the ankles, and a line of demarcation gradually formed. There

was no pulsation in the femoral arteries. Blood cultures were negative. The patient's condition did not permit operation, and on her death no autopsy could be obtained. The writer believes that in the second case the thrombus from the uterus passed through the uterine artery and thence into the circulation to the bifurcation of the aorta and occluded both iliacs, thus causing gangrene on both sides. In the first case after abortion it is thought that the venous obstruction occurred first and that the artery became later occluded. The writer has collected cases from the literature of gangrene after childbirth, abortion, during pregnancy, and after gynecological operations. He adds a case contributed by Lilienthal, of New York. This patient, aged twenty-eight years, thirteen years previously had an abortion followed by septic infection. She had subsequently been operated upon for dysmenorrhea and four months before entering the hospital the appendix and right ovary had been removed and ventral suspension had been performed. An exploration of the upper abdomen was made at this time. Ten days after this operation there was sudden pain and tingling in the ends of the fingers of the left hand. Two days later dry gangrene of the fingers and end of the thumb developed. The patient had lost weight and when admitted to the hospital was in a much depressed condition. She had severe gastric symptoms, and there was stomatitis and vaginitis which gradually disappeared with cleanliness. All four fingers of the left hand were mummified. The urine was normal. There was no pulse in the left radial artery and none in the brachial until near the axillary, where feeble pulsations could be made out. The heart sounds were normal. Blood-pressure was 114 and 87. Under nitrous oxide and oxygen anesthesia the fingers were amputated and several spurting vessels had to be tied. No flap operation was made and the thumb was not operated upon. Wassermann test showed + + reaction. The patient grew steadily worse and the roentgen-ray showed obstruction in the upper part of the jejunum. Entero-enterostomy was performed and vomiting ceased. The patient gradually failed and died. There were no signs of peritonitis. At autopsy there was a patch the size of a quarter of a dollar in the aorta close to the ventricle, and adherent to this was an organized clot, part of which had undoubtedly broken off and clogged the brachial artery. On examination aortitis was present, and in view of the positive Wassermann findings syphilis suggested itself as the possible cause. In 53 of the cases the lower extremities were both affected 15 times; the left 16; the right 15. In 1 case both hands, both feet, the tip of the nose, and portions of the ears were gangrenous. In 2 cases there was gangrene of an arm and a leg. After abortion there were 3 cases of gangrene of the lower extremities and 1 in which both were affected. Gangrene in the upper extremities in puerperal cases is comparatively rare, as but 10 cases are reported. After gynecological operations but 5 cases were collected. These had all been abdominal sections. In most of the cases some lesion of the heart or vessels was present and very rarely a patent foramen ovale seemed to be the cause. Typhoid fever, pneumonia, and pleurisy preceded gangrene in some cases. Puerperal fever and obliterative endarteritis were present in 1 case and severe puerperal sepsis treated by abdominal hysterectomy was present in another. General septic infection occurred but rarely and pyemia but once. In 6 cases gangrene

complicated eclampsia and in 2 puerperal mania. Some of the cases occurred suddenly and without known cause, and there seemed to be no connection between the general health of the patient, the type of labor, and the occurrence of gangrene. So far as prevention is concerned, whatever brings the patient into good general condition at the time of labor is certainly indicated. Aseptic precautions for the patient and antiseptic precautions for doctors and nurses are imperative. At labor hemorrhage should be prevented and the circulation disturbed as little as possible during obstetrical operations. When the condition develops and the patient is sufficiently strong to endure the operation, amputation must be promptly performed.

Leukocytosis in Pregnancy, Labor, and the Puerperal Period.—Baer (*Surg., Gynec. and Obst.*, November, 1916) reviews the literature of the subject, and gives the results of their investigations illustrated by charts. They find that there is a leukocytosis of pregnancy appearing in the ninth month especially noticeable in primiparæ but slight in amount. In labor among primiparæ there is marked leukocytosis averaging 18,255, and this is increased when labor is prolonged beyond twenty-four hours. In a second labor it is less and in and after a third labor very greatly diminished. The height of the curve is reached on the first day of the puerperal period, after which there is a constant and rapid decline, until at the tenth day the curve is about normal. Lactation has little influence, nor has age excepting in young primiparæ who have a higher leukocytosis than older women. A differential study shows that the leukocytosis is caused chiefly by the polymorphonuclear neutrophiles, with a return to normal about the third day, and absence of eosinophiles in about half of labor cases and their reappearance on the first day of the puerperal period. Large and small lymphocytes, mast cells, and transitional types show no abnormality.

Cesarean Section through the Lower Uterine Segment.—Costa (*Semaine méd.*, 1916, xxii, 552) dates this method to Jorg, of Leipsic in 1807, and Osiander, Ritgen, in 1821 demonstrated the extraperitoneal method. In 1870 Thomas, of New York, published his paper on the subject. In 1907 there were before the profession seventeen distinct operations. The author divides these into extraperitoneal and transperitoneal. The first was founded on anatomic study, but the second arose from the fact that during the performance of an operation it was often impossible to make the operation an extraperitoneal one. Franck published his first 7 cases in 1904 and Selheim, Latzko and others have improved the method. Accidents are more numerous by the extraperitoneal route, and it is estimated that the peritoneum is opened in about 20 per cent. of cases. Next in frequency is injury to the bladder in 3 per cent. Fixation of the uterus to the abdominal scar has been observed, and this facilitates uteroflexion. Such adhesions are present in about 25 per cent. of the cases, but do not always cause dystocia in subsequent labor. Many believe that the principal indication for section through the lower segment is presence of infection, and when one remembers how readily the peritoneum is opened and communication thus established with the peritoneal cavity it becomes evident that in cases of infection this is not the safest method. Selheim treated 6

cases of placenta previa and Hinkel one without entering it. Most operators, however, believe that this method cannot compare with delivery through the vagina in appropriate cases nor with the classic Cesarean section. It is thought that conditions which contra-indicate the classic section, such as threatened rupture of the uterus, incomplete rupture of the lower segment, pulmonary tuberculosis, meningitis, and pelvic tumors, indicate the operation. The writer believes that after this operation the scar is better, and that there is less likelihood of rupture of the uterine scar in subsequent confinements than after the classic section. The best statistics of maternal mortality give 5.33 per cent., with an operative mortality ranging from 4.20 per cent. to 2.87 per cent. Postoperative complications occur in about 30 per cent. Fetal mortality varies from 1 to 3.62 per cent. Statistics would indicate that the section had an advantage of about 2 per cent. in mortality over the classic section, but many believe that this apparent advantage occurs because the classic section is performed with faulty technic.

Application of Anoci Association to Obstetrics.—Hoag (*Surg., Gynec. and Obst.*, November, 1916) believes that nitrous oxide and oxygen anesthesia is safe in labor and has obtained good results by using also limited amounts of scopolamin during the first stage. He injected novocain and quinine-urea into the perineum, and observed good results from this. He believes this combined method should be of value.

Perineal Anesthesia in Labor.—King (*Surg., Gynec. and Obst.*, November, 1916) uses a 2 per cent. solution of novocain with $\frac{1}{3}$ minim 1 to 1000 solution adrenalin hydrochloride to each cubic centimeter. The site of injection was sprayed with ethyl chloride before the needle was introduced. The injection was made near the Colles fascia and in the ischiorectal region, midway between the anus and the tuberosity. The injections were made bilaterally, and in primiparæ only the anterior injections were employed. Multiparæ required both. There were no bad results in one hundred cases. Superficial necrosis of the inner portion of the labium occurred which cleared up without harm. The anesthetic was given in a few minutes and was prolonged for from two to four hours. Lacerations were diminished in number, hemorrhage was lessened, sterilization of the tissues was made more easy, and repair of injuries was greatly facilitated.

Retractions of the Uterine Muscle Associated with Obstructed Labor.—Hicks (*Brit. Med. Jour.*, October 14, 1916) describes the case of a primipara, aged thirty years, short in stature, who went into spontaneous labor. The fetal head remained high above the pelvic brim and freely movable, the head seemed half extended. The os gradually dilated, but was not filled by the presenting part. The attending physician applied the forceps, but traction failed to bring the head into the pelvic brim. A second application some time later also failed. On the next morning a third application of forceps was unsuccessful. The pelvic cavity was measured digitally, the sacropromontory was high up, the diagonal conjugate $4\frac{1}{4}$ inches, and a diagnosis was made of rachitic, flat, and generally contracted pelvis. On introducing the hand

a thick band of uterine muscle had formed around the neck of the child. The patient lived some distance from a hospital, and under deep chloroform anesthesia the attempt was made to pull the fetus through the contracted ring. The skull was perforated and traction made with the cephalotribe, with the result of wedging the whole mass more firmly into the pelvic brim. Accordingly, Cesarean section was done, the patient in a cyanotic and collapsed condition and dying on the following day. The writer draws attention to the danger of contracted pelvis where there is no apparent deformity to attract the attention of the physician. With regard to treatment, he states that if the practitioner thinks there is room enough, the fetal head being high above the brim and movable, the patient may be placed deeply under chloroform and morphin and the forceps applied. He believes that to apply the forceps to a fetal head movable and high above the brim is an obstetric operation requiring the most careful consideration, and should only be undertaken after careful examination of the condition of the uterine muscle around the neck of the fetus. If the examining hand can be passed easily beyond the shoulders of the fetus, an attempt to deliver with instruments can be made. If there is the least evidence that the uterine muscle is retracted around the neck of the fetus, Cesarean section should at once be performed. This is the old and familiar line of reasoning which continues to cause the death of mother and child. The application of the forceps to the unengaged and floating head is absolutely contra-indicated under all circumstances. With a pelvis of sufficient size and nearly normal proportions when the child is not large, podalic version is sometimes indicated. When attempts at delivery have already been made, craniotomy is to be chosen if the pelvis is sufficiently large to permit the extraction of the fetus after craniotomy is performed. If there is reason to believe that the uterus is infected, abdominal section followed by hysterectomy with the stump left outside the peritoneal cavity is indicated. No more dangerous mistake can be made in obstetric practice than the application of the forceps to the high and unengaged head.

The Scope and Limitations of Modern Obstetrics.—In the *Journal of the American Medical Association*, October 14, 1916, are published two papers, one by Davis and the second by De Lee, in which the former states the scope and limitations in modern obstetric surgery and urges that the general practitioner perfect himself in diagnosis and abstain from attempts to perform obstetric operations where the conditions are not favorable nor proper and without the necessary experience and appliances. Statistics are quoted which show that difficult delivery through the vagina by forceps or version and extraction has a higher mortality than elective section in clean cases. While in skilled hands delivery by abdominal section has a distinct and successful field, this is only possible in cases in which no previous efforts have been made at delivery and when complicated cases are referred at once to competent obstetricians. De Lee condemns unjust and unnecessary interference in labor. He cites the injuries produced by pituitrin, the indiscriminate employment of anesthetics of various sorts, the improper use of the forceps and the indiscriminate application of Cesarean section to improper cases. He urges the advantage of rectal examination for diagnosis during labor.

GYNECOLOGY

UNDER THE CHARGE OF

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Does Spontaneous Healing of Renal Tuberculosis Occur?—In view of the opinion held by practically all surgeons today that a tuberculous kidney should always be removed if the opposite organ is uninvolved and there are no positive contra-indications to operation, the possibility of non-operative cure is a question of very real importance. It is of course well known that a type of what may be called healing does occasionally occur by means of "autonephrectomy," the kidney being entirely destroyed as a functionating organ by being transformed into a mere shrivelled mass of fibrous tissue. A patient in whom this has occurred is therefore no better off, with regard to functional renal tissue, than one who has had a surgical nephrectomy, but has been exposed for a much longer time to the dangers of a chronic tuberculous focus in the body. A quite extensive investigation has recently been made by YOUNG (*Surg., Gynec. and Obst.*, 1916, xxiii, 395) to determine if there is any evidence on record to show that a definitely tuberculous focus in a kidney may undergo complete cure without total destruction of the kidney itself. By "cure" he means a complete destruction of the focus so that no living tubercle bacilli remain; he does not consider it enough that a caseous area be completely surrounded by a wall of fibrous tissue, however dense, so long as the centre is not completely organized, since it has been proved that as long as caseation exists the possibility of further infection remains. As proof of such a healing process taking place we can accept, he says, nothing less than operative or autopsy evidence of a characteristic organized tubercle or collection of tubercles taken from the kidney of an individual who showed during life tubercle bacilli and evidence of renal inflammation coming from that kidney. Apparent clinical cures, such as cessation of vesical irritability with disappearance of pus and demonstrable bacilli from the urine, cannot be accepted, as the possibility of long remissions with subsequent outbreaks in these cases is too well known. Practically all authors who have followed their cases long enough report trouble sooner or later, even after apparent cure for as much as eighteen years. The author has been unable to find after careful search a single case recorded in the literature that could be accepted as an instance of cured tuberculosis without complete destruction of the kidney, nor is he able to report one from the genito-urinary service of the Massachusetts General Hospital, thus thoroughly confirming the opinion that the only definite cure for renal tuberculosis is nephrectomy.

Oxygen in Cystography and Pyelography.—In an attempt to find some substance for casting a roentgen shadow of the bladder that would be less irritating than the silver preparations, GRANGER (*Am. Jour.*

Roentgenol., 1916, iii, 351) says that he hit upon the use of oxygen, and has been employing this gas with great satisfaction since 1909. It is well borne by the bladder, even in cases of cystitis and irritable bladder, and calculi are shown with remarkable clearness in organs distended in this manner. The entire outline of the bladder is distinctly visualized, and if the walls are unyielding from adhesions or infiltration this is easily seen; growths of the bladder, diverticula, and other deformities are also easily diagnosed. The technic is very simple. The bladder is emptied with a catheter, and a tube from the oxygen apparatus is then attached to the catheter. The bladder is distended slowly under a pressure of about one pound, until the patient feels that it is full, when the flow is interrupted for a few seconds, to be resumed at intervals until the intravesical pressure is about two pounds. The catheter is then removed and the picture taken. The author says that he has recently been trying the same method for pyelography, and reports two cases in which the results, though by no means perfect, give promise for the future after the technic shall have been further worked out. The chief points in using oxygen for the demonstration of the kidney pelvis are the correct preparation of the bowel so as to have it free from gas, and the determination of the exact amount of pressure to be used. It is important that the bladder should be kept under a slightly higher pressure than the renal pelvis, in order to prevent escape of the oxygen through the ureter.

The Pessary Treatment of Retroversion.—The choice of treatment for most retroversions has long been settled, as Reynolds (*Boston Med. and Surg. Jour.*, 1916, clxxv, 830) very justly points out, in favor of operation rather than the pessary. In the majority of cases the latter is merely palliative and not curative, and the prolonged use of the instrument is dangerous if not frequently removed and cleaned, and even if properly cared for it is in many ways more objectionable than any but the patients realize. As a rule the prolonged use of a pessary is worse than an operation, and is only tolerable when the latter is for some reason inadvisable. Moreover, the majority of retroversions are associated with inflammatory or other conditions which can be relieved only by operation. There is, however, one important class of patients in whom the author thinks great good can be accomplished by the use of pessaries, *i. e.*, those women in whom an uncomplicated retroversion occurs after childbirth in spite of a fairly intact pelvic floor, and in whom the uterus is freely replaceable. In these cases the vagina is usually capacious, the uterus somewhat heavy, and all the tissue relaxed. If these women are left alone after labor, the muscular structures which support the uterus, and which undergo evolution and involution with it in pregnancy and the puerperium, will cease involution at a degree of length and relaxation which results in an absence of tension, *i. e.*, in a comfortable adjustment of tensions in whatever position the uterus may be. If this has been held in retroversion by its own weight and intra-abdominal pressure during involution, this is the position in which it will remain, and subsequent reposition will not cause further shortening and stiffening of the ligaments sufficient to hold it there, once their course of involution has ceased. All that is necessary to secure the necessary

puerperal involution of the supporting structures, however, is to arrange the puerperium so that they undergo *complete* involution while the uterus is held in the extreme forward position. Under these circumstances the supporting structures almost invariably shorten and resume firmness to a degree which will hold the uterus permanently in a normal position. To accomplish this, the author advises starting treatment at a period in the puerperium when the uterus is still too large to be capable of retroverting, *i. e.*, from the tenth to the fifteenth day. At this time the uterus should be thrown into strong anteversion bimanually, and a carefully fitted hard-rubber pessary made to hold it there. Such a pessary will usually be larger than a stock size, and may have to be specially procured. Very hot vaginal douches should then be administered twice daily under very little pressure, to avoid the danger of carrying anything into the uterus through the dilated cervix. In most cases involution will take place so rapidly under this treatment that within a week the first pessary will be too large and too highly curved, and should be replaced by a smaller one, which in turn will have to be replaced by a still smaller one in ten days to two weeks. The hot douches are continued until the uterus is nearly down to the normal size and firmness. The author says that he has found this method nearly always successful in the class of cases described. It must be applied carefully, however, and demands a reasonable degree of experience and skill in the use of pessaries.

Studies of the Menopause. — An attempt has been made by Culbertson (*Surg., Gynec. and Obst.*, 1916, xxiii, 667) to determine some of the factors which may underlie the subjective phenomena at times associated with the natural or artificial termination of the menstrual process. The author has based his observations on the experiences of others, as recorded in the literature, and on the careful study of about 30 cases from his own practice, choosing so far as possible only patients in whom gross lesions, such as tumors, inflammations, and other factors leading to excessive hemorrhage, were absent. Like all other investigators, he has found the subject exceedingly complex, but considers that it fundamentally resolves itself into a study of the interrelationships of the entire system of ductless glands. The withdrawal of the secretion of one or more of these will be followed by glandular discord, and this is what happens at the climacteric, due to cessation of the ovarian secretion. The varied series of pictures presented by different patients passing through this period are explained by the predominance or subjection of different units of this complex glandular system in individual cases. Thus many present pictures resembling hyperthyroidism, a few suggest myxedema, and in others a tendency is manifested toward acromegaly, to dystrophia adiposogenitalis, etc. The climacteric, then, is a monoglandular affair only in its etiology; in its manifestations it is polyglandular. As the ovary decreases in activity the thyroid may maintain its full power, or may decline to a greater or less degree, and even become definitely deficient also, thus resulting in a positive or relative hyperthyroidism or a hypothyroidism as the case may be. The hypophysis and adrenals may also show characteristic disfunction, variously modifying the clinical pictures. In some cases the pineal or parathyroids may enter into

the situation; in short, the menopause may present as many different aspects as there may be single glands, or combinations of glands, working together in harmony under the influence of the ovarian hormone, or out of harmony during its absence. One important factor is nearly always present, in the author's experience, in cases of subjective menopausal disturbances, but has attracted apparently little attention. This is increased blood-pressure, which was definitely present in all but 4 of his cases. While the arterial tension is elevated, it is unstable, rising and falling under relatively minor influences. It presents one other peculiarity, that the diastolic does not go so high proportionately as does the systolic, giving a characteristically irregular but universally increased pulse-pressure. This disproportion he noticed even in the 4 cases without hypertension. He believes that the increased tension is probably due to a functional overefficiency on the part of the pituitary and adrenal glands following cessation of the ovarian activity. If this be true it would be natural to expect that the administration of corpus luteum extract would neutralize the pressor substances and decrease tension. This in fact seems to be the case, and the author has had excellent results from the employment of corpus luteum in many instances. He uses only the extract obtained from ovaries of pregnant animals, believing this to be much more efficient than that from ovaries selected haphazard. He has found that the blood-pressure not only shows a consistent and gradual decrease, but the systolic and diastolic pressures tend to come into normal relation. Where metrorrhagia was present it ceased with the reduction of arterial pressure in all cases in which the uterus was normal. The author emphasizes the importance of frequent blood-pressure estimation in these cases, both as a means of measuring the degree of menopause disturbance and of controlling the therapy. An occasional reading is of no value for this purpose, but the tension should be determined at frequent intervals, preferably daily, until improvement is well under way.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Artificial Purification of Oysters.—WELLS (*Public Health Reports*, July 14, 1916, Reprint No. 351) states that the problem of purification of polluted oysters is quite an important one as shell-fish, depending

largely for their food upon substances washed down by rivers, grow in bays and waters which in many cases receive the sewage from cities. From various investigations, it has been demonstrated that oysters are naturally cleansed when put in clean surroundings, and Phelps found that two days' sojourn in pure water was sufficient to cleanse the oysters. This fact was further demonstrated by the author by which he found that oysters inoculated with B. coli were cleansed in a few days, showing that the period necessary for purification was short enough to make the process economically reasonable. Studies of the physiology, feeding habits and digestive mechanism of the oyster showed that the food material progressed through the gastro-intestinal system and was eliminated within five hours. The successful treatment of public drinking water with a small amount of hypochlorite of lime, and the low cost of the same suggested its use for purifying oysters. A tank was filled with Chesapeake Bay water, and about forty oysters were suspended eighteen inches below the surface in iron wire baskets. The tank was inoculated with cultures of B. coli, and after the oysters had become thoroughly infected, samples were collected. The water was then disinfected with from 25 to 150 c.c. of a 10 per cent. suspension of commercial calcium hypochlorite. After six hours, a second dose was added to kill such bacteria as might have escaped the first treatment. In the quantitative estimation of the number of B. coli suitable dilutions of the material were inoculated into lactose bouillon. Fermentation of this medium with typical appearance when smeared on endo-plates was considered a positive test for the organism. The score of three separate tests on each sample of five oysters was used. The results of these tests at about 26° C. and with a definite amount of available chlorine added per million parts of water showed great purification within twenty-four hours and some change when tested after six hours. Most of the initial samples were grossly contaminated; after the action of the hypochlorite, all but one (which received only one treatment) had less than 10 B. coli per cubic centimeter. No change in the condition of the oysters could be detected nor did the disinfectant appear to interfere with the normal activity of the oysters or with their flavor. The author concludes with the statement that the experiments go to prove that oysters can be artificially purified by exposure for a short period to water containing calcium hypochlorite and that such a process is feasible and practical.

Hemolytic Streptococci Found in Milk.—The attention of workers has been directed to the pathogenic properties of streptococci found in milk because of the relation existing between the milk supply and epidemics of streptococcal sore throat. As far as is known all streptococci causing epidemics have been of the hemolytic type, causing on human blood agar a clear zone 1 to 3 mm. in diameter about the colony. Non-hemolytic or feebly hemolytic streptococci, such as Streptococcus lacticus, may cause mastitis in cows, but there is no evidence to prove that they are pathogenic for man. Davis (*Jour. Infect. Dis.*, August, 1916, xvii, No. 2) made a study of hemolyzing streptococci obtained under various conditions from samples of pasteurized and certified milk. The strains isolated were subjected to various tests and compared with human hemolytic streptococci; 328 specimens of bottled

milk were collected from nine different dairies. Human blood agar was used in making plates and the counts were made after incubation at 37° C. for forty-eight hours; 85 of these samples yielded streptococci of the strongly hemolytic variety and these were carefully studied as to their morphology and cultural characteristics. They were found to vary considerably in shape, arrangement, sugar fermentation, and in the characteristics of the hemolytic zone formed. They were found to be more resistant to heat than the human strains of streptococci. Most of the strains were relatively avirulent for rabbits and therefore throat epidemics are very virulent for rabbits. It was found that human hemolytic streptococci coming direct from human lesions or from the diseased udder of a cow are much more virulent for cow than the hemolytic milk strains or bovine types, and a study of the morphology and cultural characteristics of the human and bovine types helps to prove further the difference between these two types. There has been no definite evidence to prove that the hemolytic milk streptococci have any sanitary significance although, on the other hand, the data at hand are not sufficient to positively exclude the possibility of bovine streptococci attaining virulence for man. However, during the course of this investigation, the different strains were observed for a considerable time and under various conditions, but only very slight, if any, variations were noted.

The Correlation of Certain Reactions of Colon Bacilli and Like Organisms with Source.—Hutton (*Jour. Infect. Dis.*, 1916, xix, No. 4) studied forty-five members of the colon-aërogenes group of bacteria isolated from various sources: milk, human feces, rabbit feces, water, sewage, human urine, and from egg powder. Their fermentation powers with various carbohydrates, lactose, sorbite, raffinose, dextrin, dextrose, saccharose, dulcite, mannite, maltose, adonite, and inulin were tested and it was found that there is a better correlation between saccharose-fermentation and source than between saccharose-dulcite fermentation and source. The methyl-red and Voges-Proskauer reactions are related as all organisms alkaline to methyl red gave a positive Voges-Proskauer reaction and all organisms acid to methyl red gave a negative Voges-Proskauer reaction. Organisms that gave a positive Voges-Proskauer reaction were non-fecal in origin and therefore it seems that this and the methyl red reactions are of sanitary importance in determining colon organisms of fecal origin.

The Bacteriology of the Bubble Fountain. — Pettibone, Bogart and Clark (*Jour. Bacteriol.*, 1916, i, No. 5) found that during an epidemic of streptococcus tonsillitis in a woman's dormitory at the University of Wisconsin streptococci were present in the bubble fountains used in the building and in the water issuing from these fountains. The city water supplying these fountains is of excellent quality, obtained from deep wells in sandstone, and several examinations showed no evidence of streptococci, while smears from a Berkefeld filter, through which the city water flowed for one week, showed nothing. A survey of all the fountains of the University showed the presence of Gram-positive streptococci in 55.8 per cent. of these fountains—an almost pure culture being obtained from one. Tests were

performed on an experimental bubbler in the laboratory, which was of the ordinary continuous flow type, the bubble being fed through four perforations in the top of a cylinder which screws into the centre of a hollow metal bulb. When B. prodigiosus was introduced by a pipette or the moistened lips into such a fountain, organisms were found to remain in the column of water from two to one hundred and thirty-five minutes, depending partly on the height of the bubble. This was due to the fact that, of the organisms introduced, most of them are flushed off at once, but some remained "dancing" in the water of the column for varying periods of time. The authors recommend the use of a fountain with the tube at an angle of 50 degrees from the vertical to avoid the difficulties of the fountain with a vertical column. Plates made from this type of fountain never showed the presence of B. prodigiosus even when samples were taken immediately after cultures of it had been introduced.

Experimental Epidemiology in Tuberculosis.—A. DISTASO (*Jour., Infect. Dis.*, 1916, xix, No. 4) studied the epidemiology of tuberculosis and formed the following postulate: The longer a community of people has been in contact with tuberculosis virus the less mortality is to be found among the people constituting that community, though almost 90 per cent. of civilized people in postmortem examination present healed tuberculous lesions. The author says that in investigating the cause of this diminished mortality two questions arise: (1) whether the virus has become attenuated through passages, or (2) whether the persons concerned have acquired a resistance to the virus. In answering these questions the author considers these problems—how the tuberculosis process is spread, what are the probable channels of infection, and what are the conditions under which resistance or immunity are established. In a series of experiments, uninfected guinea-pigs were put in the cages with infected ones at regular intervals. After seventeen days of exposure 75 per cent. died and showed tuberculous lesions on postmortem examination. By a second experiment the author showed that the amount of the initial dose of tubercle bacilli does not materially affect infection by contact, that infection by contact in 100 per cent. of the cases is lethal, and that the conditions of infection are still active after one month and three days. Another series of experiments was undertaken to determine the period of infectivity of the virus. As a result of these, the author concludes that a cycle of infection through contact exists. There is a curve which is *nil* at the beginning, which rises to its highest point between the ninth and thirty-third days and which then goes down again. It would seem that "at the beginning of the process few tubercle bacilli are excreted, with which the new contact can easily deal, and acquire a kind of resistance which preserves the animal when the excretion is at its height; but as soon as the infection goes on and the microbes swarm in the body, massive doses are excreted." By this time the new contact is powerless to cope at once with this large quantity, and therefore the pathogenic process establishes itself. The author's experiment to find out whether guinea-pigs living for a long time in contact with tuberculous guinea-pigs acquire a state of immunity proved nothing, as the subcutaneous inoculation was too severe a test for

demonstrating immunity. As regards the channel of infection the author states that in contact cases of tuberculosis in guinea-pigs three hypotheses, namely, that infection occurs (1) through the mouth, (2) through the nose, or (3) through both. He believes that the channel of infection in guinea-pigs is through the nose, as his experiments show that very small doses given through the nose almost certainly produce pulmonary tuberculosis, whereas observation of habits of the guinea-pig show that infection through the mouth probably does not occur.

PATHOLOGY AND BACTERIOLOGY

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The Cytology of the Exudate in the Early Stages of Experimental Pneumonia.—EVANS (*Jour. Infect. Dis.*, 1916, xix, 440) publishes a brief report of an experimental study of the early cellular exudate in acute pneumonic infections. In classifying the cells, which is done according to their origin rather than by morphology, the writer makes use of the indophenol blue reaction, employed to demonstrate the presence of an oxydase ferment in the cell body. Rabbits were used in the experimental work. Pneumonia was induced by intratracheal injections of broth cultures of pneumococci of Groups I and IV and two types of streptococci. The pneumococcus infection gave the gross appearance of lobar pneumonia better than did the streptococci. The lesions were examined after intervals of from eight to thirty-six hours following injection. Tissue from three autopsies on human cases of pneumococcal pneumonia, in which death had occurred at the third, fourth and fifth days respectively, was also available. The fact that the cytology of the exudate in the human cases was quite like that of the experimentally induced exudates is notable and indicates with what success such experimental work may be carried on. The cytology was also practically the same in all the experimental preparations. The cellular elements of the exudate were largely mononuclear although alveoli in which polymorphonuclear cells largely predominated were sometimes found. A few small lymphocytes were always present. A few very large mononuclear cells which were readily classified as epithelial cells also appeared frequently. In addition to these, two other types of large mononuclear cells were present in about equal

numbers. These two types were best differentiated by the indophenol blue reaction for the presence of oxydase ferment. The type showing the presence of the ferment strongly suggested the transitional mononuclear leukocyte (Naegeli), although some resembled myelocytes. The other cells, without oxydase ferment, were considered lymphoid in origin. Their resemblance to the so-called polyblasts (Maximow) is noted. The plates accompanying the article illustrate clearly that differentiation between the large mononuclear types without the use of the oxydase reaction would be quite impossible. Careful examination of a given field, before and after the oxydase reaction should make the distinction a fairly simple matter.

Spontaneous Amebic Dysentery in Monkeys.—Eichhorn and Gallagher (*Jour. Infect. Dis.*, xix, 395) report an epidemic of amebic dysentery in monkeys. The lesions found resembled in many respects those of human tropical dysentery. The animals were spider monkeys (ateles ater) from Central America. One animal when received from Columbia was ill with symptoms similar to those later manifested by the others. It was assumed that this animal carried the infection. Though the food and care which the animals received were of the best, their close association in the same cage and in addition a perverted appetite for their own excrement accounted for the transmission of the infection. The particular species of ameba dealt with was not determined. The organisms were seen both in the vegetative or ameboid forms, and in encysted forms. The former were most numerous in liver abscesses, though also seen in the intestinal contents where the encysted forms were in greatest numbers. It is pointed out that the encysted stage is usually obtained in the intestinal tract, and is a later stage of the life cycle of the organism. The liver abscesses showing the vegetative form were considered as more recent lesions. Transmission experiments were undertaken with cats, which have been successfully inoculated with the ameba histolytica, the cause of tropical dysentery in the human. These inoculations were, however, without result, although feces containing many encysted ameba were given in quantities that should have assured success. There is, however, good evidence that the ameba, since it was isolated from the intestinal canal in every case and from the liver abscesses, is an important etiological factor if not the only one in the cause of the disease. The early symptoms were lassitude, weakness, indifference and some loss of appetite. Emaciation was not marked. A severe diarrhea was the principal manifestation. The feces were fluid, yellowish gray and very offensive. They were blood stained in the more acute cases. The severe cases lasted only two or three days, while others lived for as many weeks after the onset of symptoms. Fifteen monkeys were exposed. Eight out of the fifteen died, and one of nine showing symptoms recovered. The protocols of the eight deaths are given individually In all, the cecum and colon were the seat of the most marked lesions. The rectum was involved to a variable extent. The lesions never passed the ileocecal valve. The mesenteric lymph nodes were sometimes enlarged and edematous. In two cases, liver abscesses were present. The mucosa of the large bowel was covered by a dense corrugated mass of grayish granular necrotic material. When less severe, there were isolated ulcers with raised, irregular congested

borders and gray, depressed, necrotic bases. The destruction of the mucosa occurred without fibrosis or cellular exudate in the deeper tissues, but when the submucosa was invaded, mononuclear leukocytes and a dense fibrous wall infiltrating the adjacent mucosa were characteristic. Amebas were found in the mucosa and in the necrotic tissue surrounding the ulcers. The liver abscesses were multiple in one case, while in the other but a single abscess was seen. The abscesses were without a fibrous wall, except where they approached the capsule of the liver. The borders of the abscesses were surrounded by a zone containing small, irregular necrotic areas. The abscesses burrowed deeply, and spread out within the interior of the lobes. Their interior was a mesh-work of liver-structure in all stages of disintegration. They contained a grayish white fluid pus, in which many amebas showing protoplasmic movement were seen. The authors suggest the possibility of transmission to the human as well as to laboratory animals of amebic dysentery, both by frankly sick monkeys and by others acting as carriers without, at the same time, showing any evidence of disease.

The Bacteriology of the Urine in Lobar Pneumonia.—In a short paper, accompanied by a concise and interesting chart, MATHERS (*Jour. Infect. Dis.*, xix, 416) reported the result of cultures made from catheterized specimens of urine obtained from cases of pneumonia in various stages of the disease. The research of Fraenkel and Rieche on pneumococcus in the kidney, in which they reported the finding of pneumococci in 22 out of 26 cases studied, is cited. In beginning the work, the questions as to whether pneumococci were commonly found in the urine of pneumonia patients, and whether, if found, the organisms had suffered any change during their passage through the kidney, were especially considered. After obtaining the specimen aseptically, a small portion, after centrifugalization, was examined both unstained and in stained smear for casts, leukocytes, bacteria, and other pathological elements. Cultures were made by plating the sediment from 10 c.c. of urine on human blood agar. These plates were then incubated at 37° C. for twenty-four hours. By cultural methods, pneumococci were isolated from the urine in 10 out of 26 cases. Gram-positive diplococci were seen in smears from the sediment in 18 of the 26 cases. These were doubtless other types of cocci, as staphylococci were frequently found, or possibly they represent dead pneumococci. The latter is possible, since urine is a poor medium for the growth of pneumococci. The organisms were all identified by the use of specific sera in addition to the usual differential reactions. Of the ten strains found, five belonged to Group I, three to Group II, and two to Group IV. Pneumococci were isolated from the blood and sputum of the cases studied; these corresponded in all the major characteristics to those obtained from the urine of the same case. Minor morphological differences, considered insignificant by the author, were found between the pneumococci from blood, sputum and urine in a given case. As to other organisms, two streptococci, one hemolytic and one of the viridans group were isolated; staphylococci and diphtheroid bacilli were found in several instances. The period immediately before or after the crisis was the most favorable one for the isolation of pneumococci from the urine. The writer concludes that during a

pneumococcic infection in the respiratory tract, pneumococci may be excreted in the urine. They appear to bear no definite relation to other pathological elements in the sediment; the strains isolated from the urine are in all essentials like those found in the blood and sputum. Hence, the deduction is made that urinary cultures may be of great value in the diagnosis of pneumonia, and of pneumococcic infections generally.

Antibody Productions by Typhoid Vaccines.—Stoner (*Jour. Immunol.*, 1916, i, 511) attempts to solve the problem concerning the value of the different kinds of typhoid vaccine. He shows by a review of the literature that the experimental results of different writers do not agree as to the efficiency of the different vaccines. Not only does the production of (1) agglutinins, (2) opsonins, (3) bacteriolysins, and (4) precipitins vary in individuals or animals inoculated with these differently prepared vaccines, but also the results obtained by various experimenters. Stoner used for his experiments three types of vaccine. The first was the usual emulsion of twenty-four-hour agar cultures in saline and killed by heat. The second was prepared in a similar manner, save that before inactivation the bacteria were treated with antityphoid immune serum for three hours at 37.5° C. and then for twenty-four hours in the refrigerator. The third was prepared and treated with serum in a similar way to the second; then the organisms were killed with absolute alcohol, washed, dried *in vacuo* over sulphuric acid, and then ground in a mortar and emulsified in saline. These three vaccines were used to immunize both rabbits and humans. Sera of all cases were tested, after immunization, for agglutinins, opsonins, and bacteriolysins. It was found in both humans and animals that the first, or non-sensitized, vaccine stimulated a much more potent agglutinating serum. The opsonins and bacteriolysins, however, were slightly more marked after the use of either of the other two vaccines. Considering these results, and in view of the fact that experiments by Bull have proved the agglutination to be an important factor in the immunity, the author concludes that the sensitized vaccines are in no way superior to the non-sensitized. He states that though our knowledge of the mechanism of typhoid immunity is very scant, and that even after the disappearance of the demonstrable immune substances a potential immunity is still present to a certain degree, we still must give some weight to the presence of these substances in the blood. Thus on account of these substances and from lack of other evidence to prove the greater efficiency of the newer types of vaccine the author recommends the non-sensitized vaccine in all cases.

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ORIGINAL ARTICLES

THE ROLE OF FAT IN DIABETES.[1]

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The work with diabetes at the Hospital of the Rockefeller Institute began with feeding experiments on partially depancreatized dogs, and since then has grown in various directions. The results have been applied in the treatment of human cases, and this side of the investigation has been taken up by Drs. Stillman and Fitz, Dr. Stillman having studied especially the carbon dioxide changes in alveolar air and blood and Dr. Fitz the acetone bodies in blood and urine. It was a great good fortune when Dr. DuBois consented to determine the respiratory metabolism of certain patients at the Russell Sage Institute, and thus (in connection with the similar findings of Benedict and Joslin) some facts were established which were important for the intelligent application of the clinical treatment, and some theoretical questions decided and some others opened up. On the side of the animal experiments, Dr. Palmer has carried out a research in the practically unknown field of the sugar-content of the tissues under normal and various pathological conditions. Dr. Perlzweig and Miss Wishart are assisting in several problems, comprised chiefly under the topic to be discussed. The combination of animal and clinical work is very advantageous, each throwing light on the other. Also, the animal experiments are different from the customary, in that they do not consist in brief observations limited to a single point, but, on the

[1] Harvey Society Lecture, November 4, 1916.

contrary, animals are brought into the desired diabetic or other condition, and then are studied like human patients, through months and years if necessary. This plan has always appeared to me as indispensable for real progress in certain aspects of this problem. Acute experiments cannot give the best picture of chronic disease. Chronic conditions in animals need to be studied by the same combination of clinical, chemical, and microscopic methods as used for human patients, and for the same reason, namely, that one part of the picture can be understood only in relation with the other parts. On this plan, information is gained by determining the means to produce in animals the conditions occurring spontaneously in patients, and then by studying these conditions with the freedom and accuracy which are possible in animal experiments.

The problems of diabetic and normal metabolism are being opened up with surprising rapidity as methods become available. The monograph concerning my research at Harvard was written in 1912, and at that time comparative analyses at frequent intervals as shown in these charts were impossible, because the methods then existing required too much time or material. The present work was done entirely with methods published by American chemists within these few years. The numerous blood-sugar analyses were made possible by the method of Lewis and Benedict, which was used unmodified as originally described. The analyses for acetone bodies were carried out first with a modification of the methods of Shaffer, Marriott, and Folin and Denis, and later by the recent Van Slyke method. The alkaline reserve of the plasma was estimated by Van Slyke's simple and accurate device of the carbon dioxide combining power, which has proved its usefulness both experimentally and clinically. The blood-fat was determined by Bloor's method in the modification employed by Murlin and Riche. The methods introduced by Sellards and by Levy, Rowntree and Marriott deserve mention in connection with the study of acidosis, but had to be omitted in this research. It is evident that various blood and urine examinations, calorimetric studies, tissue analyses, and histologic and other investigations are most instructive when performed not upon different animals but upon the very animals for which these other data exist.

It has been decided to discuss the role of fat in diabetes because of its theoretical and practical importance, and because it has constituted one of the most confused and perplexed phases of the subject, where any light from any source may be deemed desirable. The feeding experiments mentioned at the outset have included the feeding of fat, and this has involved the longest and most difficult experiments of the series. Therefore, this opportunity is taken to present the results of some of the experiments in this direction, and this paper will consist largely of observations not heretofore published.

It was formerly impossible to make a satisfactory study of this question with animal experiments because only two types of diabetic animals were known, namely, the Minkowski type, with total extirpation of the pancreas, and the Sandmeyer type, with removal of most of the pancreas and isolation of the remainder from its duct communications, so that the blocking of secretion brought on sclerosis and atrophy. Neither of these types of animals is capable of digesting and absorbing enough fat for the purpose, or of affording in other respects a sufficiently close reproduction of human diabetes, where there is ordinarily no deficiency of pancreatic digestion. I have previously described a method which gives a good approximation of the clinical condition. Those familiar with the publication will recall that this consists in removing most of the pancreas, leaving a remnant ordinarily of one-eighth to one-twelfth always communicating with a duct. With the smaller remnants the diabetes is severe; with the larger remnants it is mild; but by feeding the animals beyond their tolerance, so as to maintain a prolonged glycosuria, there is progress downward, as in human cases, and the mild diabetes becomes as severe as that which follows the more extensive removal of pancreatic tissue. For our present purpose and for most purposes the best results are obtained by having the pancreas remnants as large as possible, for two reasons. One is the avoidance of cachexia. The totally depancreatized dog dies within a relatively brief period, while an equal loss of sugar and nitrogen caused by phloridzin is far better borne. Some dogs with very small pancreas remnants do fairly well, but a large proportion of them fail to thrive, gradually emaciate, and die; whereas dogs with larger remnants but equally severe diabetes thrive much better. Nothing is known concerning the nature of this peculiar pancreatic cachexia; presumably it represents metabolic failure. The second reason referred to consists in the power of digestion. The digestion of the partially depancreatized dogs is never quite equal to the normal. Some of the diets used tax the digestion of normal dogs. In particular, the larger the pancreas remnant the better do the dogs dispose of a high fat diet. Occasional dogs become diabetic with exceptionally large pancreas remnants, and such animals are valuable for this use. In general, the program is to chooose young dogs as strong and as voracious as possible. The pancreatic tissue removed is the minimum required to produce mild diabetes. The tolerance is then broken down by overfeeding, the diet sometimes including several hundred grams of glucose daily until the desired degree of diabetes results. The animals are then often kept free from glycosuria for several weeks or months, and any tendency to recovery of too high a tolerance is checked by a period of overfeeding. In the best cases there is thus a decided hypertrophy of the acinar tissue, so that the remnant may come to equal as much as one-

fourth of the original weight of the pancreas, and yet the diabetic condition is maintained. Such dogs have highly satisfactory vitality and digestive power, and are very well suited for the fat feeding and other experiments. Though the internal secretory function has thus been injured largely by functional means, it remains fairly constant at its low level, and any recovery of tolerance is exceedingly slow. In this respect the animals resemble human patients. There is a difference in that the functional overstrain in dogs results in actual anatomical desctruction of cells in the islands of Langerhans, while such an anatomical effect in human patients is still doubtful.

The role of fat in diabetes will be discussed in its relation to three subjects.

I. Lipemia.

The first of these is lipemia. Here we deal with the disposal of fat from its absorption by the bowel to its taking up by the cells of the body. A few words may be devoted to the normal process, which is still obscure in essential points. An early dispute concerning digestion has been settled, since it is established that fat is not absorbed in emulsion as such but only as the split products. In the intestinal epithelium the glycerin and fatty acids are recombined into neutral fat. Some earlier researches, especially those of Rosenfeld and others in the dispute over fatty degeneration and infiltration, led to the view that this recombined fat is identical with the food-fat; that is, that only the fat synthesized from carbohydrate or other foods can be peculiar to the species, while otherwise the fat of the body takes its character from the fat of the food. A series of authors, Bloor being the latest, have modified this extreme view, and have shown that the epithelium changes and rearranges the constituents to considerable extent, so that the recombined fat differs from the food-fat in being more nearly like the natural fat of the animal. The procedure of splitting and recombination therefore apparently serves for the absorption of useful fats, the exclusion of non-saponifiable substances such as mineral oils, and the partial modification of the absorbed fat to resemble the specific body-fat. Some of this recombined fat is perhaps taken up in the blood capillaries and carried in the portal circulation to the liver. But at least 60 per cent. of it is known to enter the lacteals and pass in fine emulsion through the thoracic duct into the systemic circulation. Obviously, it cannot linger long in the blood, which would be hopelessly overloaded by the fat of a single meal. The cells remove it rapidly, so that, notwithstanding the heaviest intake, the blood-fat like the blood-sugar varies only within narrow limits. In the phraseology of Magnus-Levy, the level of the blood-fat must represent the balance between inflow and outflow at any given time.

This brings us to the consideration of the fat content of normal blood.

There have been described three physical forms in which fat may exist in the blood. First may be mentioned the occult form, which ordinarily predominates. The fine emulsion of the chyle is changed as it enters the blood stream. The droplets apparently dissolve, so that the clear blood plasma contains fat which cannot be colored by osmic acid or any fat stains or extracted by ether or other solvents, and can only be demonstrated by digesting the proteins with enzymes, acid, or alkali, or precipitating them with reagents such as alcohol. This fat is probably non-dialyzable and seems to exist in some colloid combination. The second form consists of surplus or less soluble fat, in microscopic droplets, the blood-dust or hemoconia. These can be stained with fat stains and extracted with fat solvents, and as they increase they make the plasma first turbid and then milky, as in digestion lipemia. The third possible form of fat is perhaps never normal. It is the form described by several authors when the plasma is cloudy or even opaque, yet cannot be cleared by the centrifuge; tiny droplets may or may not be visible under the microscope, but the substance is not colored by fat stains or dissolved in ether or chloroform. Boggs and Morris reported over 4 per cent. of this form of fat in the blood in anemic lipemia of rabbits. Bloor found that this form arises *in vitro* when certain abnormal (viz., diabetic or anemic) bloods are allowed to stand, the previously clear plasma becoming turbid. The three physical forms are presumably due to varying proportions and combinations of fats and lipoids among themselves, and possibly with proteins, salts, or other substances. Normal fasting plasma is clear and, according to Bloor, contains approximately 0.29 to 0.42 per cent. fat in human beings, and somewhat more, viz., 0.51 to 0.66 per cent. in dogs. Turbidity may appear within about an hour after a fat meal; it reaches its maximum in about six hours, and after twelve hours the plasma is again clear. The susceptibility to alimentary lipemia, in other words the balance between the digestive function and the assimilative function, differs in different species. Nothing is known concerning differences in the rate at which their tissues can take up fat. Rabbits are resistant to alimentary lipemia, and increasing the dose of fat merely causes diarrhea (Neisser and Bräuning). Sakai proved that rabbit blood has no unusual capacity for carrying concealed fat. Therefore it is possible to accept the explanation of Kreidl and Neumann, based on dark-field examinations of hemoconia, that intestinal absorption of fat is much slower in herbivora than in carnivora; but the question has not been investigated chemically, and offers a promising opportunity for the use of the new micromethods. The goose has such a digestive power that it can be enormously fattened by forcible feeding; and in the serum of such stuffed

geese Bleibtreu, also Hervson and Sedel, found some 6 per cent. fat, though the rye used in Bleibtreu's feeding contained only 1.5 to 2.5 per cent. fat. Stuffing geese with fat-free food did not cause lipemia. Man and the dog are intermediate between these extremes. Alimentary lipemia between 1 and 2 per cent. is probably the highest that ever occurs in normal human subjects. Munk and Friedenthal found as high as 3 per cent. alimentary lipemia in dogs. It is impossible to produce in dogs a lipemia equal to that of the stuffed goose by any quantity or duration of fat feeding, for the digestion breaks down before any such plethora is produced in the metabolism.

Thus far the word fat has been used in the old-fashioned sense, indicating the whole of the ether-soluble constituents. But aside from the neutral fat, which preponderates, and the soaps and free fatty acids possibly occurring in small quantities, there are constantly present the substances called lipoids, grouped under the titles lecithin and cholesterol. Such phosphatids and sterols exist in every living cell; they are evidently of the most indispensable importance somehow, but their function is practically unknown. Even the gross metabolism of lecithin and cholesterol is mostly unknown. They can be absorbed as such from the bowel and also synthesized by the body. Cholesterol especially is excreted through the bile and feces. The nervous system is rich in these substances, and the liver, the red corpuscles, and the adrenal cortex have all been claimed to play a part in their metabolism. Bloor finds that the lecithin and cholesterol are each about a third of the total ether-soluble extract of normal blood. Their ratio is fairly constant and remains so in most pathological conditions, suggesting an important relationship. The quantity of glycerides in the fasting plasma might possibly be zero, which would mean that the entire transport of fat would be in the form of lecithin and cholesterol esters; but a small quantity of simple fat is probably present. Digestion of fat brings an increase in the glycerides.

Both lecithin and cholesterol rise in most forms of lipemia. Lecithin is markedly increased in alimentary lipemia even though the ingested fat be practically free from lecithin. Terroine, Hagenau and others observed a similar parallelism between fat and cholesterol even when the food fat was extremely poor in cholesterol; and Sakai laid down the rule that there is no lipemia without cholesteremia, supposedly because of the solubility of cholesterol in fat; and Gardner and Lander have pointed to an absorption of cholesterol from the bile; but Bloor has found no change in the cholesterol during alimentary lipemia. The occurrence of the lipoids free or in esters or other compounds may have special significance, but this is unknown at present.

The relations in plasma and corpuscles also deserve notice. Normally, according to Bloor, lecithin and cholesterol are nearly

equal in the plasma; the lecithin content of the corpuscles is approximately double that of the plasma, and also double the cholesterol of the corpuscles. Bloor assumes that two-thirds of the plasma cholesterol is combined in esters. It is believed that all the cholesterol of the corpuscles is free. The corpuscles contain no true fat or only indeterminable traces.

Comstein claimed that the presence of red corpuscles is necessary in order for the fat to be changed from the emulsified to the soluble form. Munk and Friedenthal asserted that the corpuscles actively take up fat, so that in alimentary lipemia they may contain a higher percentage than the plasma. Bloor has confirmed this statement, and furthermore has found that lecithin increases chiefly in the corpuscles and only slightly in the plasma. Following up the idea of Loew and of Leathes that all fat is utilized *via* lecithin, Bloor has set up the hypothesis that all or most of the absorbed fat must be taken into the corpuscles and converted into lecithin before it can be assimilated. He finds here an explanation of the arrangement whereby fat is led into the general venous circulation to be thoroughly mixed with the blood before being carried to the liver or any other capillary domain for assimilation. Since lecithin is increased in a brief lipemia, as during digestion, he assigns special importance to it in the early stages of assimilation; and as cholesterol is increased in lipemias of long standing, he ascribes importance to it in the later stages of assimilation of fat.

The actual mechanism by which cells take up fat is unknown. Authors from Hanriot to Rona and Michaelis, Caro and Sakai have undertaken to demonstrate a lipase function. The process in assimilation would thus correspond to that in digestion. But the alleged lipase is so feeble that its presence or activity is hard to determine accurately by titration, and recourse is had to delicate physicochemical tests with the stalagmometer. Also, it seems truly characteristic of the subject of diabetes that the attempt should be made to explain lipemia by diminution of lipase, disregarding the extreme diminution of lipase in diseases without lipemia, as reported, for example, by Bauer. The lipolytic enzyme of blood seems classifiable with the glycolytic enzyme as accidental and unimportant, and the notion of enzymatic digestion of fat in the blood plasma or at the cell boundary does not merit serious consideration. On the other hand the conversion of fat into the plasma-soluble form, through the process supposed by Bloor or any other process, appears as a significant phenomenon. All living cells contain a similar "masked" or combined fat, and the most plausible view is that fat passes through the cell boundaries in this colloid or soluble form. Taylor refers to this as the "metabolic" form of fat. Nevertheless, it must be borne in mind that we are dealing with hypotheses throughout, and that nothing

is known positively concerning the means by which the cells take up fat from the blood.

Except after meals it seems probable that hyperlipemia is abnormal like hyperglycemia. A slight lipemia accompanying exercise was observed by Murlin and Riche. Bloor suspects that excitement may increase blood-fat as it does blood-sugar. Animals possessing stores of fat show a slight lipemia during fasting, supposedly because of increased transport of fat. Bloor's highest figure was about 0.9 per cent. Slight lipemia may occur in pregnancy, but according to studies by Klinkert and others, cholesteremia is the most prominent feature, and is responsible for the occasional xanthelasma and possibly related to the accompanying hypertrophy of the adrenal cortex. Just as hyperglycemia, so also hyperlipemia may occur in various metabolic disorders. It may be found in obesity, alcoholism, and nephritis. Chauffard and Grigaut described hypercholesteremia in nephritis. According to Lauber and Adamuck, Zinsberg and Chauffard the white flecks in the retina in nephritis are largely accumulations of cholesterol esters, and (Borberg, Landau) cholesterol is increased in the adrenal cortex. The familiar accompaniments of nephritis, namely, atheroma of bloodvessels and the arcus senilis of the cornea, likewise represent deposits of cholesterol esters. J. Müller reported an unusual case of nephritis, with chylous hydrothorax, and the above-mentioned opacity of the plasma which cannot be cleared by the centrifuge or fat solvents or stained with fat stains. Here the blood contained over 3 per cent. total fat, and 0.6 to 0.8 per cent. each of lecithin and cholesterol. Cholesteremia and lipemia are present with icterus, gall-stones, and liver disease, as shown by Klinkert and Beumer and Bürger. Cholesterol is deposited in the xanthoma formations and the cholesterol content of the bile is said to be increased. Lipemia has also been reported in pneumonia, heart disease, dyspnea, syphilis, and esophageal cancer, some of these cases being perhaps mere alimentary or inanition lipemia. The lipemia in a number of other conditions named by Fischer is doubtful. Experimentally, slight lipemia occurs in poisoning with phosphorus, phloridzin, and other drugs causing fatty degeneration, and during and after narcosis, though the phenomenon is inconstant (Murlin and Riche, Bloor, Lattes and others). Fat emulsions injected intravenously are rather promptly disposed of by the liver and other tissues, and lipemia is resisted. Bloor's highest figure after such injections is 1.5 per cent. blood-fat. It is well known that intoxication with fatty acids has been suspected in the etiology of some clinical anemias. The analyses of Freund and Obermayer, Erben, and Beumer and Bürger show lipemia absent in pernicious anemia and some cases of leukemia, and in other cases of leukemia a slight lipemia up to 0.7 per cent. Bloor gives similar findings in pernicious anemia, with the sugges-

tion that the low cholesterol values may be significant in view of the protective action of cholesterol against hemolytic agents. Boggs and Morris observed lipemia in a man with anemia secondary to hemorrhoids. They compared it with lipemia which they discovered in rabbits made anemic by repeated bleedings; they found no lipemia in cases of equal anemia produced by pyrodin poisoning. In the anemia of phenylhydrazin poisoning, Sakai described lipemia of approximately 1 to 3 per cent.; and as observed by Underhill, fatty liver and hypoglycemia accompany such poisoning. When the anemia was produced by bleeding, Sakai found values almost up to 6 per cent. blood-fat, with proportional increase of lecithin and cholesterol. These are the highest figures ever reported for non-diabetic lipemia.

We come now to the principal metabolic experiment which nature has performed for us, namely, diabetes. Just as there is no other way of producing hyperglycemia equal in intensity and duration to that of diabetes, so also the lipemia present in some cases of diabetes is beyond parallel in any other clinical or experimental condition. In blood taken from a thirteen-year-old diabetic child three days before death in coma, Frugoni and Marchetti reported a total ether extract of 27 per cent., and in blood from the same patient at autopsy 34 per cent. The highest figures fully accepted by German authors are 19.7 per cent. by Neisser and Derlin and 18.13 per cent. by B. Fischer. For comparison it is interesting to note that the highest known value for fat in thoracic duct chyle by Zawilsky, with maximal fat feeding in dogs, was only 14.6 per cent. Sakai reckoned that the blood in Fischer's case contained over 700 grams of fat. There are numerous reports of all grades of lipemia below this. Imrie has described one of the most recent cases, with over 14 per cent. fat in the blood. The most comprehensive chemical study has been made by Bloor, who gives complete analyses in thirty-six of Joslin's patients. He found the blood-fat normal or even subnormal in mild cases, but always increased in severe cases, ranging up to twice the normal. Two untreated cases showed the typical excessive lipemia, one with 2.9 per cent. and the other with 11.2 per cent. of fat in the plasma. Such lipemic blood looks like cocoa and the plasma like cream. Tyson's 1881 text-book and Joslin's 1916 text-book both devote the frontispiece to lipemia, the latter showing the appearance of the blood and plasma, the former depicting the fundus of the eye, for the condition is so marked that it can be recognized by intraocular examination. Normal urine contains a trace of fat, and this is increased in lipemia, Frugoni and Marchetti's case showing 0.088 per cent., Imrie's case 0.1 per cent., and Neisser and Derlin's case the unusual figure of 0.8 per cent. urinary fat.

For closer understanding, inquiry may be made first as to the nature of the fat circulating in such excess in these cases. Analyses

from Fischer to Bloor show that the great mass of it is neutral fat. Klemperer and Umber's claim that both lecithin and cholesterol are increased out of proportion to the neutral fat and their suggestion of the name lipoidemia instead of lipemia have been overthrown by more recent work. The lipoids are increased, but the higher the lipemia the greater is the predominance of the true fat. Imrie agrees with some earlier authors in finding lecithin relatively low in diabetic lipemia. Bloor has shown that lecithin varies somewhat in parallel with the total fatty acids until marked lipemia is reached, then falls markedly behind in relation to both these and cholesterol. The striking increase in cholesterol has been noted by authors from Fischer onward. In Imrie's case the blood contained 1.5 per cent. cholesterol. Bloor's case with 2.9 per cent. lipemia had 0.5 per cent. cholesterol and his case with 11.2 per cent. lipemia had 1.26 per cent. cholesterol. There is evidently a remarkable activity of cholesterol metabolism. The liver is generally bright yellow, but Fischer remarked that the liver cells did not contain large fat-drops as in ordinary fatty livers. The Kupffer cells like the endothelia elsewhere are stuffed with fat, and Kawamura found that this fat consists not merely of glycerides but cholesterol esters, which he claims the Kupffer cells normally refuse to take up. Jastrowitz undertook to study lipoid infiltrations in the fatty livers after various poisons. Beumer and Bürger described a case of diabetes in which an oat-cure cleared up the existing lipemia, but the cholesterol persisted at three times the normal figure. Klinkert states that the white spots in diabetic retinitis represent accumulations of cholesterol esters which may clear up considerably under treatment. The apparent thickening of the vessels of the fundus of the eye in lipemia is due to the opacity of the plasma and also to the cholesterol ester infiltration of their walls. Xanthomata are an expression of hypercholesteremia in diabetes as in other conditions, though other factors must be concerned. Von Noorden saw them clear up under treatment and return with aggravation of the diabetes. Bacmeister in one case furnished rather doubtful evidence that the cholesterol excretion in the bile may be markedly increased in diabetes. Of other compounds it may be noted that Imrie reported 0.38 per cent. of fatty acids present in the blood as soaps. Aside from the anemia-producing effects, fatty acids and their soaps are highly toxic, Munk finding that 0.11 to 0.13 gram oleic acid as soap injected intravenously in thirty to forty-five minutes suffices to kill rabbits by heart-block. Lipemic patients show no more anemia or intoxication than other diabetics, so it would seem either the findings of high percentages of circulating soap are mistaken or other substances present must protect against its poisonous action. In survey, therefore, it may be said that diabetic lipemia is characterized by an increase of lecithin, which becomes rela-

tively deficient as the lipemia becomes excessive; but comparison with other forms of lipemia is difficult, for it seems probable that if alimentary or any pathological lipemia could be raised as high as diabetic lipemia the relative deficiency of lecithin might be similar. Analyses on stuffed geese would be interesting. Diabetic lipemia is also characterized by a much greater increase of cholesterol, almost parallel with the fat, in excess of anything ever observed outside of diabetes, and in direct contrast to what occurs in alimentary lipemia.

Another contrast is seen in the corpuscles, for instead of the increase which occurs in alimentary lipemia, their fat content amid the tremendous lipemia of diabetes remains normal. Bloor finds the same to be true in other forms of pathological lipemia. The entire chemical picture is interpreted by Bloor as follows. The component which becomes more predominant as the lipemia increases is the true fat, which is the inert form of fat, and its accumulation indicates that the fat is not being properly prepared for assimilation. Likewise the relative deficiency of lecithin and the lack of fat in the corpuscles indicate that the corpuscles are not performing their function of transforming fat into lecithin, as in the earlier phase of assimilation. The high cholesterol figures are taken to mean that a later stage of the process is represented in this lipemia and that the cholesterol mechanism has not failed. Beumer and Bürger concluded that a considerable part of the cholesterol is free and not in esters, and in Imrie's case practically the whole of the cholesterol was found to be free. This fact might be significant if generally confirmed. Throughout it must be remembered that the entire subject is in the stage of hypotheses, but they are interesting as such and represent a real beginning in attacking the problem.

A second point for inquiry is the source of the fat in lipemia. In alimentary lipemia it is sufficiently obvious that the fat is derived from the food, but the lecithin, aside from what may come from the food, must be supplied by the body. In the various forms of pathological lipemia, lecithin and cholesterol must presumably be supplied by the body; this was certainly true in Müller's case of nephritic lipemia, in which the patient had been on lipoid-poor diet for months. In the anemic lipemia of rabbits, Boggs and Morris showed that the tendency to alimentary lipemia was increased, but yet the essential source of the blood-fat was the body-fat, for the lipemia developed on a diet of bread and grass, the animals rapidly lost weight, and in extreme emaciation the lipemia ceased. Because of the high lipoid content in diabetic lipemia, Klemperer and Umber concluded that the condition represents an increased breakdown of body cells, since only these could furnish so much lecithin and cholesterol. This explanation seems foolish when applied to a lipemia of 10 to 20 per cent. Several

authors have followed the hypothesis that the lipemia is derived from the body fat. Magnus-Levy has upheld the opposite view that the blood-fat is derived from the food, that the fat is taken up from the intestine and poured into the blood as usual, but there is some obstacle to its leaving the blood, either a physicochemical difference in the fat itself or a change in the cells or in the capillary walls; and that the huge quantities sometimes found in the blood may result from slow accumulation. Neisser and Derlin's patient with 19.7 per cent. blood-fat had very little body fat. They compared the iodin and Reichert-Meissl numbers of the fats in the food, chyle, blood, and several tissues and concluded that the blood-fat comes from the food. Imrie considered that the 300 grams or more of fat in the blood of his patient was too much to be derived from the food; the iodin number of 73 for the fatty acids of the blood compared well with 68 for the adipose tissue, but differed widely from that found in liver, heart, and kidney; he therefore concluded that the lipemia represents mobilization of connective-tissue fat. Bloor observed extreme lipemia only in two patients who had been eating excessive amounts of fat, while severe cases under treatment with restriction of fat as well as other foods seemed to show the tendency but the figures were moderate. Accordingly, he considered that the lipemia is derived from the food and is due to ingestion of fat beyond the capacity of a weakened assimilative function. It is to be regretted that very few fat determinations have yet been carried out on our patients at the Rockefeller Institute Hospital. The gross observations agree with the experience of Bloor and Joslin that even the most creamy plasma clears up under treatment. One extremely emaciated man showed a diminishing but still opaque lipemia through six days of fasting, which disappeared only gradually in the subsequent treatment. The exit of fat from the circulation must therefore be very slow in some cases. It should be considered a therapeutic duty to clear up a pathologic lipemia.

Dogs are subject to diabetic lipemia, as shown by an observation of Gerhardt mentioned by Naunyn, of 12.3 per cent. blood-fat in a dog with spontaneous diabetes and pancreas necrosis, which is the highest lipemia ever recorded in a dog. It is impossible for a dog to have more severe diabetes than that following total pancreatectomy, but the plasma generally is almost or quite clear. In an exceptional instance Seo observed lipemia of 2.4 per cent., with increase in lecithin and cholesterol. It is possible that Seo's dog was fat and that Gerhardt's dog had been eating fat. The facts perhaps indicate that the lipemia does not represent mobilization of tissue fat by the intense metabolic disturbance, unless to some extent in a fat-rich animal, but that on the contrary it mostly represents deficient assimilation of fat, and that depancreatized dogs with their maximal diabetes show little lipemia

because in them the deficiency in assimilation is balanced by the deficiency in digestion of fat.

This supposition can be tested in dogs of the type described at the outset, which have severe diabetes along with satisfactory digestive power. It is found that they are in fact subject to diabetic lipemia in its full intensity. These dogs have been fed suet, which is not the most easily or rapidly digested form of fat; but approximate determinations in our first case indicated lipemia rivalling that of Gerhardt. The tables show some values incidentally observed in connection with other work. Here is a sample of plasma from a child entering the Institute Hospital in coma. It contains 11 per cent. fat. The analyses made thus far show wide differences in the curves of fat in the blood of normal, phloridzinized, and diabetic dogs after identical feedings. The minor fluctuations will require further study, but the outstanding feature is the disproportionate increase in the diabetic animal. Granting severe diabetes, the lipemia varies largely with the digestive power. The record of Dog 396 (Table I) shows how the lipemia fell as the digestive power failed and the plasma became clear. These figures represent analyses twenty-four hours after feeding. On withdrawing fat from the diet lipemia clears up in from one to several days, according to its intensity, as seen in Dog 345 (Table III). A possible exception to this rule may occur in a type of fasting acidosis to be described later. In the terminal state of Dog 280 here depicted (Table II) gross observations gave the impression of an increase of blood-fat up to the development of a marked lipemia on fasting, but the opacity of the plasma was the only index, and this chance for a decisive verdict concerning the possible occasional origin of diabetic lipemia from body fat was lost through inability to carry out the necessary analyses.

The production of diabetic lipemia in dogs is a simple matter, but it opens opportunities. Here we have the means of flooding the body with fat in a manner unparalleled outside of diabetes, of making and unmaking this abnormality easily and quickly. The first result is the conclusive proof that the lipemia is derived ordinarily from the food-fat. It will be a simple matter to feed a variety of fats and compare with the blood-fat in the different cases; some information concerning fat assimilation may thus be gained, and we may be able to report such experiments later. But the simple fact that the lipemia appears so readily on feeding fat and ceases so promptly on omitting fat suffices to settle the dispute concerning its usual origin.

It is expected to publish later some analyses of the lipoid content of the blood and various organs, but this phase must be omitted at this time. As far as comparison is possible between Seo's analyses of liver tissue in diabetic lipemia and those of Jastrowitz and others of fatty livers produced by various poisons, no indica-

TABLE I.—DOG 396 (PARTIALLY DEPANCREATIZED).

Date, 1916.	Blood ‡						Urine.							Weight, kg.	Diet.	Remarks.
	Plasma sugar, %	Hb., %	CO_2, capacity.	Total acetone,* mgm. per 100 c.c.	Lipemia, qual.	Total fat, plasma %	Volume, c.c.	Total acetone,* mgm.	Sugar, gm.	Total nitrogen, gm.	Ammonia nitrogen, gm.	N : NH_3-N ratio.	D : N ratio.			
Aug. 16–17	0.465	102	..	..	0	0.509	1313	761.6	50.55	24.10	1.97	12.25	2.10	..		
17–18	0.327	96	57.6	..	0	0.512	1358	614.8	59.70	22.80	..		2.62	11.16	1000 gm. lung.	
18–19	0.400	85	42.4	..	0	0.516	1430	344.9	58.40	25.40	2.58	9.85	2.30	10.90		
19–20	..	..	..	..	0	..	1290	443.8	71.50	22.60	1.74	13.00	3.16	..		
20–21	0.356	104	36.2	33.9	0	0.586	1220	873.5	67.20	23.80	1.83	13.00	2.82	10.80		
21–22	0.384	103	..	12.5	++++	1.752	410†	111.4	19.20	5.77	0.45	12.80	3.33	10.70		Eats entire diet taking suet first.
22–23	0.324	98	46.2	29.0	++++++	1.600	804	405.2	24.92	11.58	1.36	8.52	2.15	10.82		
23–24	..	..	..	..	..	..	985	425.5	26.35	11.20	1.88	5.95	2.35	10.86		
24–25	0.285	59	48.1	70.8	++++++	0.835	860	359.9	31.85	10.50	1.37	7.66	3.03	10.70		
25–26	..	..	..	..	..	..	915	786.9	19.08	11.30	1.10	10.30	1.68	10.80	400 gm. lung; 200 gm. suet.	
26–27	..	..	..	..	..	..	782	297.1	26.00	10.95	3.98	2.75	2.38	..		
27–28	0.268	39	32.8	97.8	+	0.445	1018	260.6	24.20	10.15	..	..	2.38	10.75		Growing weak; fatty diarrhea.
28–29	0.385	64	30.9	57.5	0	0.533	922	191.8	26.40	8.64	1.37	6.30	3.06	10.25		Diet forced; vomited; 5 gm. sod. bicarbonate.
29–30	..	..	..	..	0	..	720	123.8	30.00	10.30	2.74	3.76	2.91	10.20		
30–31	0.294	45	38.6	67.0	0	0.365	1020	..	24.40	9.50	4.40	2.16	2.57	10.17		
31–Sept. 1	..	..	..	..	..	..	938	..	24.10	6.60	3.00	2.20	3.65	..		Moribund; killed.

* Total acetone bodies as acetone. † Incomplete specimen. ‡ Blood drawn twenty-four hours after feeding.

TABLE II.—DOG 280 (SEVERE DIABETES).

Date.	Blood.				Urine.					Remarks.
	Plasma sugar, %	Hb., %	CO_2, capacity.	Lipemia, qual.	Total nitrogen, gm.	Ammonia nitrogen, gm.	N : NH_3-N ratio.	Sugar, gm.	D : N ratio.	Diacetic acid.	
Aug. 11–12	..	..	..	..	3.07	0.930	3.30	6.35	2.07	+++++	Fasting.
12–13	0.345	70	24.2	+++++	15.21	3.66	4.16	37.92	2.50	+++++	
13–14	0.435	70	29.0	++++++	7.19	0.50	14.40	7.66	1.06	+++++	Bicarbonate. Death.

TABLE III.—DOG 345 (PARTIALLY DEPANCREATIZED).

Date.	Weight.	Blood.‡ Plasma sugar, %	Hb. %	CO_2, capacity.	Acetone, qual.	Lipemia, qual.	Total fat, plasma %	Urine.† Volume, c.c.	Acetone, qual.	Total acetone,* mgm.	Total nitrogen, gm.	Ammonia nitrogen, gm.	N : NH_3-N, ratio.	Dextrose, gm.	D : N ratio.	Diet. Remarks.
June 8	11.25	0.232	112	..	0	0	0.92	..	..	..	..	..	..	..	..	
9	..	..	..	..	0	++++	..	778	+++	43.6	6.900	..	..	70.79	..	
10	..	0.276	109	..	0	++++	3.88	880	+++	80.1	6.432	0.730	8.80	73.30	..	
11	..	..	..	..	..	..	..	835	++++	48.4	3.932	..	..	39.83	..	
12	10.5	0.228	110	..	?	0	2.42	562	+++++	25.9	3.844	0.612	6.26	43.27	..	200 gm. lung; 100 gm. bread; 100 gm. suet.
13	..	..	..	..	+	..	..	764	+++++	10.7	4.769	0.609	7.85	34.63	..	
14	..	0.213	108	50.0	+	+++++++	7.12	1270	..	58.4	5.092	0.531	9.58	65.65	..	
15	10.75	0.333	112	57.6	+	++++++	6.00	940	++	..	5.038	0.394	12.80	64.95	..	
16	..	0.313	106	..	..	+++++	2.27	985	..	..	9.600	0.610	15.72	61.56	..	
17	..	..	..	..	..	..	..	990	..	..	6.672	..	..	61.87	..	
18	..	..	..	..	..	..	..	732	..	..	4.721	0.490	9.65	48.82	..	
19	10.85	..	..	..	..	..	..	1180	..	94.0	3.327	..	..	49.08	..	
20	..	..	..	..	..	..	..	598	..	35.9	2.738	0.203	13.42	44.35	..	200 gm. lung; 100 gm. bread; 150 gm. suet.
21	..	..	..	..	..	..	..	1370	..	..	5.918	0.479	12.38	59.59	..	
22	..	0.244	90	..	++++	++++++++	3.16	1810	++++++++	1042.6	5.249	0.796	6.60	78.73	..	Unwell.
23	..	..	..	..	..	..	..	1270	++++++++	812.8	6.731	0.792	8.50	68.58	..	
24	..	..	..	..	..	..	..	2090	..	1097.3	3.762	0.501	7.55	58.30	..	
25	..	..	..	..	..	..	..	915	..	657.8	6.405	0.602	10.66	67.71	..	
26	..	0.238	93	38.5	..	+++	3.79	590	+++++++	367.0	4.838	0.489	9.88	40.45	..	100 gm. lung; 100 gm. bread; 100 gm. suet.
27	..	..	..	..	..	..	..	804	..	313.6	3.939	0.426	9.26	64.32	..	
28	10.82	..	..	..	..	..	..	1285	..	..	4.011	0.552	7.26	75.68	..	Unwell.
29	..	..	..	..	..	..	..	620	..	282.7	2.852	0.303	9.40	47.74	..	
30	10.65	0.213	96	40.4	..	+++	..	690	+++++++	298.1	3.008	0.324	9.26	43.20	..	
July 1	..	0.222	97	..	++	+++	..	396	..	182.1	7.680	0.760	10.10	30.50	3.97	
2	..	..	..	..	..	..	..	608	..	307.8	12.800	1.137	11.21	35.90	2.80	600 gm. lung. Improving.
3	..	..	..	..	..	..	..	332	+++++++	127.2	8.370	0.713	11.78	23.90	2.86	
4	..	0.270	109	34.2	++	+++	1.53	636	..	359.3	16.250	0.850	19.11	30.60	1.88	
5	..	0.256	94	43.9	..	..	0.78	405	..	..	9.450	0.940	10.10	31.20	3.30	
6	10.3	0.323	90	36.1	..	0	0.90	830	+++++	192.6	16.600	1.930	8.60	51.90	..	
7	..	0.250	86	39.1	+	0	..	728	+++++	180.2	9.770	..	..	47.10	..	600 gm. lung; 100 gm. bread.
8	..	0.357	86	47.7	..	0	..	1585	+++++	518.3	14.300	1.100	13.00	106.20	..	Good condition.
9	..	..	..	..	..	..	..	1600	++++	488.0	15.400	..	..	94.40	..	
10	10.13	0.304	86	46.4	+	0	1.98	2025	++++	559.0	10.400	1.010	10.30	93.10	..	

* Total acetone bodies as acetone.

† Not catheterized.

‡ Blood drawn twenty-four hours after feeding.

tion is offered of any specific chemical character of the organ infiltration in diabetes. The huge amount of circulating fat and the remarkable activity of lipoid metabolism offer other opportunities which we shall not be able to follow up. The unusual quantities of cholesterol that seem to be formed invite a study of the excretion in bile and feces and other features important to those interested in cholesterol metabolism. Various problems lately under investigation by authors such as Aschoff, Landau, Mulon, and Borberg concerning the morphology and the chemistry of fats and the function of the adrenal cortex and other organs in regard to them may perhaps be studied with special advantage in a condition in which the lipoid metabolism is specially disturbed or exaggerated.

The metabolism of matter and energy has never been studied in human patients with extreme lipemia, and to avoid confusion from acidosis or other factors it is desirable to make a series of comparative observations on the same individual in the lipemic and non-lipemic condition, and this can be done most conveniently in animals. All are now familiar with the work in Lusk's laboratory, which has shown that the combustion of any food is increased as the supply of it to the cells is increased. Ingestion of any food increases the total metabolism more or less according to the kind and quantity of the food. Ingestion of fat causes alimentary lipemia and the combustion is preëminently of fat. Bleibtreu's geese, stuffed with rye, with lipemia up to 6 per cent., are said to have shown respiratory quotients as high as 1.33. Whether the figures are strictly correct or not it seems evident that values above unity were present, indicating combustion preëminently of carbohydrate and the formation of fat from carbohydrate. This means one of two things: either the carbohydrate or the general plethora inhibited the combustion of fat in spite of 6 per cent. fat in the blood—in which case Lusk's law of summation of stimuli is reversed—or if there was combustion of fat in the remotest degree proportional to the lipemia the total metabolism or the formation of fat from carbohydrate must have been tremendous. Interesting modifications of this experiment might be made by giving fat-rich instead of carbohydrate-rich diet or by using partially depancreatized geese. It is well known that in diabetic patients or animals alimentary hyperglycemia is more pronounced than normal, but the effect on the respiratory quotient is less, and in severe cases may be absent altogether, and this is one of the best evidences of deficient combustion of carbohydrate in diabetes. The case with fat is different, for diabetic patients and even totally depancreatized dogs always burn fat readily. The distinction is not absolute, for depancreatized birds—chickens, ducks, geese—show intense hyperglycemia with little or no glycosuria and can even receive considerable carbohydrate by feeding or injection and

dispose of it somehow. Their kidneys are highly impermeable to sugar, but there is a difference beyond this, for feeding or injection of sugar in severely diabetic dogs with renal impermeability means rapidly fatal hyperglycemia—possibly 2 per cent. blood-sugar. The diabetic birds do not metabolize their carbohydrate normally, for glycogen is deficient and emaciation and death occur. The mammalian kidney is almost impermeable for fat, so that lipemia cannot be checked by excretion, and the presence of acetone bodies indicates some abnormality in fat combustion. But the known abnormality consists merely in incompleteness in the end products; no experiments have ever indicated any difficulty on the part of the diabetic in attacking the fat molecule. Patients and suitable diabetic animals often go along on a certain level of marked hyperglycemia, without glycosuria, and evidently burning some carbohydrate. They seemingly require a higher "pressure" of sugar in the blood in order to accomplish the combustion of sugar. In the moderate hyperlipemia ordinarily present in severely diabetic patients, Bloor saw evidence of a similar need of increased fat "pressure" in the blood in order for the cells to burn fat. There is opportunity to test this idea with respiration experiments. In contradiction to the prevalent belief of normal fat assimilation in diabetes, investigation will probably show that a certain level of lipemia does not have equal metabolic influence in non-diabetic and in diabetic lipemic conditions. It will very likely be found that the effect on the gaseous exchange is slower and of less degree in diabetic lipemia, corresponding to the known facts concerning hyperglycemia in the milder cases, so that an alimentary lipemia of 2 or 3 per cent. in a normal animal may represent a greater activity of fat metabolism than much higher blood-fat values in an animal with diabetic lipemia. Also, it may be found that the metabolic effect varies among diabetics in proportion to their susceptibility to lipemia, and conceivably may not be fully normal in any severe diabetic. Studies of this sort will throw light on the ability of the diabetic to attack the fat molecule; they may help to show why fat-feeding seems sometimes neither to strengthen nor build up a patient; they will indicate what significance may be assigned to lipemia in the question of metabolism in diabetes; and by completing the proof that lipemia is due to deficient assimilation rather than increased mobilization of fat (even if increased mobilization sometimes occurs), they may contribute an analogy in support of the dominant belief that the hyperglycemia is primarily due to deficient assimilation rather than increased mobilization of sugar.

Our investigation of lipemia by the use of diabetic dogs to date has dealt chiefly with the problem of the actual cause of it, its relation to other diabetic phenomena and to the internal function of the pancreas, and the information which it may furnish concern-

ing the fundamental diabetic condition. Besides the origin from food-fat, certain other questions can now be definitely answered.

First, the visible fat is not in the abnormal form insoluble in ether. Seo found in his one case that the opacity was cleared by ether, and the same has been our experience.

Second, the power of plasma to hold fat in clear solution is not diminished. In connection with the hypothesis of combined sugar, I formerly suggested a possible analogy with fat, in that lipemia might be due to deficient combination of the fat, and raised the question whether the pancreas supplies anything of importance for this combination. Reicher determined the fat before and after digesting blood with pepsin-hydrochloric acid, and concluded that the latter fraction has no importance. Seo mentioned visible lipemia in only one of his depancreatized dogs, yet the blood-fat in the other instances was from 1 to 1.5 per cent. This might indicate an unusually high power of the plasma to hold invisible fat, and the same possibility seems indicated by some of our experiments, and would not be surprising in view of the high lipoid content. Accordingly, no significant reduction in the simple ability of the blood to "mask" fat has been demonstrated. On the other hand, Bloor's belief is that fat must be combined into lecithin in order to be assimilated, and that a deficiency of this combining function is present in diabetic lipemia. The facts at least suggest that methods used for testing the combination of either fat or sugar should not be too crude.

Third, the relation of fat in plasma and corpuscles is of interest especially in connection with Bloor's hypothesis. Unfortunately most of our determinations so far have had to be limited to the plasma, and only a few analyses of corpuscles have been made. Thus far they indicate low total fat content in the corpuscles. Having controllable experimental conditions, it should be possible to trace any significant alterations from the normal through the mildly lipemic animals to the extreme degree in the severely lipemic animals. This research is in progress, but it is better to omit discussion at present rather than attempt conclusions from insufficient data.

Fourth, lipemia is not due to hyperglycemia. For example, mildly diabetic animals, even with abundant fat in the diet, may be made to show extreme hyperglycemia without corresponding lipemia.

Fifth, lipemia is not due merely to absence of carbohydrate or loss of sugar from the body. Maximal phloridzin poisoning with feeding of nothing but fat, or the longest possible phloridzination on diet free from carbohydrate and high in fat, has failed to produce in dogs anything resembling diabetic lipemia.

Sixth, lipemia is not due to the presence of acetone bodies. Lipemic patients generally have acidosis, but a case of lipemia

without ketonuria was described by Beumer and Bürger. It is well known that many patients with severe acidosis and even coma show clear plasma. Bloor found "no definite relation between high blood lipoids and the occurrence of acetone bodies in the urine." In dogs it can be shown that the acidosis of phloridzin poisoning causes nothing like diabetic lipemia, that diabetic acidosis may occur without lipemia, and that marked lipemia may be present without acidosis. Maximal lipemia probably never exists without acidosis, but this is because acidosis goes with the general severity of the diabetes.

Seventh, lipemia is not due to change in the reaction of the blood. The greatest possible reduction of the carbon dioxide capacity by diabetes, phloridzination, or chronic hydrochloric acid poisoning has produced none of the characteristic lipemia.

Eighth, lipemia is not due solely to removal of pancreatic tissue within the limits mentioned. If enough pancreatic tissue is removed to produce even severe diabetes, but the actual occurrence of diabetes is avoided by diet, the characteristic lipemia does not occur. In some such cases alimentary lipemia certainly persists longer than normal, but this may represent merely a slower digestion of fat owing to the smaller supply of pancreatic juice. If the curve of the lipemia is lower as well as longer, it will indicate such delayed absorption. The characteristic of diabetic lipemia is that it both rises higher and falls more slowly than normal. When the assimilative disturbance is slight it may to some extent be balanced by the delayed absorption, so that the mere prolongation of slight lipemia becomes hard to interpret. These experiments are in progress and a sufficient number are not yet finished to permit positive conclusions. But it is certain, as stated, that the full diabetic lipemia never occurs in the absence of other symptoms of active diabetes.

Ninth, lipemia is not the result of breaking down of a hypothetical "fat function" by direct overstrain of that function. Here again tedious experiments extending over months have been involved. These experiments have proved that the heaviest and most prolonged fat diets, in normal and partially depancreatized animals, neither increase nor diminish the susceptibility to lipemia. If the conditions are such that the fat-feeding give rise to glycosuria and acidosis the lipemia begins to mount up; otherwise not.

Tenth is the question of the relation of lipemia to the severity of the diabetes. Up to the time of the present treatment which restricts fat in the diet, high lipemia has been considered a sign of very bad prognostic import. Bloor found some elevation of blood-fat in all severe cases, normal or subnormal values in mild cases. Beumer and Bürger have reported the only known instance of lipemia in mild diabetes. In dogs of the type described above, it is easy to show that the lipemia depends upon the severity of the

diabetes. The partially depancreatized dog, with relatively little tendency to lipemia as long as he is kept free from diabetes, acquires the marked susceptibility without any further operation as soon as severe diabetes is brought on by overfeeding with any kind of food. The most striking experiment is to keep the plasma continuously clear by carbohydrate or protein diet, then suddenly give a meal of fat. High lipemia is present within a few hours and persists for more than twenty-four hours. On continuance of fat diet the lipemia mounts to a point governed by the digestive power. As in human cases it is then unremitting, and like an old hyperglycemia, varies relatively little with meals. With breakdown of digestion, or on withdrawal of fat from the diet, the lipemia clears up in from one to several days, according to its intensity. The tables already referred to illustrate some of these statements.

This permits discussion of the relation of lipemia to the internal pancreatic function. There may be three possibilities: Is lipemia due to disorder in some organ or in the general system secondary to the original diabetic disturbance? is it another manifestation of deficiency of the same hormone concerned in carbohydrate metabolism? or does it represent lack of some different internal secretion of the pancreas? There is sound justification for speaking of several internal functions of the pancreas. Diabetes is not a mere glycosuria or inability to assimilate glucose. There are abnormalities in the metabolism of protein, fat, and doubtless of mineral substances which are primary and cannot be reproduced secondarily by phloridzin or any other means. But it is possible that the various functions in question all belong to one internal secretion, and this unitarian hypothesis is inherently the most attractive one. It is a plausible view that the pancreas supplies something necessary for the synthesis and maintenance of protoplasm, that deficiency of this factor makes nutrition of the cells difficult and disposes to breaking down of their reserves, and that this tendency makes itself felt in regard to all classes of foods, but earliest and most manifestly in regard to the most labile and most easily excreted forms. Only positive evidence could justify a doctrine of plurality of internal secretions of the pancreas. The unitarian standpoint would have theoretical importance, for it might reasonably be inferred that the part played by the single hormone would be similar toward the various classes of foods. Glycosuria and non-assimilation of carbohydrate—lipemia and acidosis—increased protein catabolism, aminosuria, and changes in the creatin-creatinin relation—diabetic edema and other anomalies concerning salts, all afford different lines of approach. If all alike are due to deficiency of a certain action of a single hormone, comparisons will aid in learning what the action of this hormone is, and by following the different trails it may be possible to track the thing

home and master the secret of the internal pancreatic function and diabetes.

Between the partially depancreatized animal without diabetes or lipemic tendency, and the same animal after feeding has brought on severe diabetes and susceptibility to lipemia, there is only one known anatomical difference, which consists in exhaustion and degeneration of cells in the islands of Langerhans. The fact that this alteration and the lipemic tendency come on simultaneously, and are typically produced by pure carbohydrate or protein feeding, proves conclusively that the disorder underlying lipemia is bound up to considerable extent with the other diabetic disturbance and is not entirely independent. Possible evidence for the existence of more than one internal pancreatic secretion might be found in the discovery of Lane and Bensley that the islands of Langerhans consist of two different varieties of cells, filled with granules which stain differentially; these cells are believed to be independent in origin and type and not transitional or derivable one from the other. This histological interpretation is strengthened by Homans' discovery that only the so-called Beta cells ordinarily degenerate in experimental diabetes, while the Alpha cells remain preserved even in advanced stages and show particularly dense granulation. This observation was confirmed in the work at this Institute. But it might still be possible that both types of cells are concerned merely in carbohydrate metabolism. Krumbhaar published the description of an important case of spontaneous diabetes in a dog in which the pancreas was about twice the normal size and its tissue appeared normal; and microscopic examination showed advanced degeneration of the Beta cells everywhere, along with less extreme but still marked exhaustion of the Alpha cells. Lipemia or acidosis was not found in this animal, but it apparently was not studied on fat diet. Martin has discovered that some of our experimental dogs show this same degeneration of the Alpha cells. He is following up the investigation, but there has not yet been time for enough comparisons to establish the possible significance. When a dog shows a dextrose-nitrogen ratio equal to that following total pancreatectomy, it will be interesting to know whether the Alpha cells are degenerated or not. If they are intact their part in carbohydrate metabolism will become very questionable. Material is available from animals of different species, different ages, different grades of intensity and duration of diabetes, on various diets, in nutritive states ranging from obesity to emaciation, with lipemia and acidosis present or absent, and with other physiological or pathological variations, so that it may be possible to throw some light on the function of the Alpha cells and the unity or plurality of the internal pancreatic secretion.

The facts concerning human patients must also be considered in

this connection, and the question whether the full conditions are reproduced in dogs. Granting that all patients with severe diabetes have some tendency to lipemia, is this tendency equal in all of them? When the majority of cases show fairly clear plasma, and a small minority show lipemia of 10 to 20 per cent., can it be maintained that varying quantities of fat in the diet suffice fully to explain such differences? If there is another cause for the discrepancy, does this cause consist in some additional pancreatic disturbance, or in a breakdown in some other organ or in the general system? It is unfortunate that accurate observations covering this point have not been made; but probably most physicians who treat diabetes will have the decided impression that individual variations exist, and that the majority even of severe cases on heavy fat diet are not subject to the most intense lipemia. Though it is difficult to gauge the true severity of diabetes, possibly Beumer and Bürger's patient above mentioned manifested a special susceptibility to lipemia in the presence of only mild diabetes. Several of the patients at the Institute have shown intense lipemia, and it is not evident that their condition was more severe or that they had eaten more fat than some others without lipemia. Certain patients under treatment were tested with heavy fat diets for other purposes and remained free from lipemia. On the other hand a very few incidental observations seem to indicate that when there has been heavy lipemia, and when it and the glycosuria have been recently cleared up, a meal of fat may cause the plasma to remain turbid for more than twelve hours. The suggestiveness of these chance observations is strengthened by the experience with dogs, in which such a phenomenon certainly occurs. It may prove worth while to investigate whether patients react differently to such a test and whether it signifies a specific weakness of fat assimilation.

Certain observations seem to indicate that in dogs the tendency to lipemia may vary independently of the other diabetic symptoms, and that the governing conditions are at least in part experimentally controllable. The work in progress must be carried further before it will be possible to decide positively concerning such observations or interpret their significance for the theory of diabetes. The gist of the matter to date is that diabetic lipemia has been reproduced in dogs, and there are hopes that the possible varying grades of susceptibility shown by human patients may be experimentally imitated.

II. Acidosis.

The second subject for discussion in connection with the role of fat in diabetes is acidosis. Here the primary requirement for clearness is a definition, and the one adopted may be said to rest on three bases.

The first of these is origin and general usage. The pioneer workers of the Naunyn school grasped this problem broadly and deeply; they did the principal work that has been done, and they marked out the fundamental lines which all subsequent research has followed. Hallervorden recognized the significance of the increased ammonia. Stadelmann attributed coma to acid and suggested alkali therapy; it is noteworthy that he used in this connection the term acid intoxication, not acidosis. Minkowski perceived the presence and meaning of the diminished carbon dioxide content of the venous blood. Magnus-Levy determined the balance of acids and bases in the urine. But Naunyn introduced the term acidosis, and said, "With this word I designate the formation of β-oxybutyric acid in metabolism." The name and definition received general adoption, and have been used also by the opponents of the Naunyn school who believe that the intoxication and coma represent something other than a simple shift of reaction. The more recent followers of Naunyn should not pervert his definition, which has been acceptable to both parties; and even if the word must become the exclusive property of either faction, it is not for the losers to carry off the nomenclature.

The second basis of definition is that of need and distinctiveness. Diminished alkalinity, increased hydrogen ion concentration, lowering of carbon dioxide, decrease of buffer salts, and (for the symptoms of these changes) acid intoxication—all these terms have definite meanings, and to appropriate the name acidosis for any one of them is merely to create a useless synonym. No other name but acidosis exists for the metabolic process which it denotes. Ketonuria and ketonemia have their accurate place but do not cover the ground. Possibly the word ketosis might be suggested and used for special purposes, but the change of established usage would be difficult and seems unnecessary. It may be urged that there are states of increase of other acids, lactic, phosphoric, etc. If desired it may be feasible to include these under a broad interpretation of acidosis, and to distinguish them when necessary from acetone body or diabetic acidosis. But the latter is the original and most important type, and the name acidosis belongs preëminently to it.

The third ground for the definition is its fundamental significance. Here may be seen the sound judgment of Naunyn in defining on the basis of metabolism, not of reaction. A definition must be qualitative not quantitative. Criteria of reaction vary with the tests; the finer methods of today reveal changes not formerly perceptible, and future technic may give truer appreciation of the physiological balance in the blood or may follow changes into the cells. But the metabolic disturbance in question is continuous and must be regarded as a unit. It is recognizable at a time when the protective mechanisms of the body are apparently efficient to prevent any abnormality of reaction, and it persists in spite of any dosage of alkali. Furthermore, a comparison with

typhoid fever is illustrative. Fever is a prominent feature in typhoid infection and has been embodied in the very name of the disease. Also, simple hyperpyrexia is a possible cause of death, and rightly or wrongly many physicians believe that they benefit patients and even save lives by treating this symptom with cold bathing or other measures. Nevertheless, the proper definition of typhoid fever must be in terms of infection with Bacillus typhosus and not in terms of fever. Similarly, the acid character of the products in acidosis is important and has received recognition in the name of the condition. Simple displacement of reaction may be a cause of intoxication and even death, and clinical improvement and even the saving of life may be achieved temporarily by the mere administration of alkali. But the metabolic disturbance back of it all is the real thing to be defined and comprehended and treated. A slight objection might conceivably be raised on the basis of rare cases of reported coma without acetone bodies. But there is the old-time answer that such cases though occurring in diabetes may not be diabetic coma; and there is no evidence that a definition based on reaction would fit them any better. For these reasons it seems best to retain the definition of acidosis in the original sense of Naunyn—namely, as that state of metabolism of which the presence of abnormal quantities of the acetone bodies is the one known constant characteristic.

This leads to the question of the origin of the acetone bodies. Their appearance was first ascribed to fermentation of carbohydrate, then to breakdown of body protein. More recent experiments with phloridzin and liver perfusions prove the possibility of a partial derivation from the leucin, tyrosin, and phenylalanin of the protein molecule, while the greater portion of the amino-acids form glucose, and the exact status of some of them is uncertain. But the work of Rosenfeld, Hirschfeld, Geelmuyden, Magnus-Levy and others made it apparent that the principal source of the acetone bodies is fat. The disposal of fat up to the point of its leaving the circulation and entering the cells was discussed under lipemia. Aside from storage its fate in the cells is supposedly combustion proceeding through successive carbon groups, the best accepted chemical view being the beta-oxidation hypothesis of Knoop, according to which butyric and β-oxybutyric acid may be normal intermediary products and excretion of the latter may represent merely imperfect combustion. One molecule of higher fatty acid could thus furnish only one molecule of β-oxybutyric, and Magnus-Levy calculated that the quantity thus available corresponds to the maximum known excretion, but that in some cases this demands a molecule of acetone bodies from practically every molecule of fat burned. Acetone is a secondary and chiefly abnormal product, but there is a question which of the other bodies is primary. Formerly, diacetic acid was believed to be

derived from β-oxybutyric by oxidation, but Maase, Blum, Dakin, and Marriott have brought evidence that the reverse may be true and that diacetic acid may be the primary product formed from butyric and β-oxybutyric be derived from it by reduction. The orthodox belief is that all cells, including muscle cells, burn fat directly. Von Noorden is one of the very few who imagine that the muscles can burn only sugar, which the liver forms from fat for their use, and that acetone body production is associated with the formation of sugar from fat. It is a common belief that the acetone bodies are produced largely or chiefly in the liver. In Embden's laboratory, perfused livers have been shown to form acetone, while kidney, lung, and muscle formed none; furthermore, the livers of depancreatized and phloridzinized dogs formed several times as much acetone as those of normal dogs. Also, Fischler and Kossow phloridzinized Eck-fistula dogs and found that these animals, with ligation of the portal vein and drainage of the portal blood directly into the vena cava instead of through the liver, showed less ketonuria than ordinary dogs likewise receiving 1 gram of phloridzin daily; but with the reversed Eck-fistula, that is, with ligation of the vena cava and drainage of its blood together with the portal blood through the liver, the ketonuria was increased above that of the controls. The experimental evidence thus seems strong, but it requires criticism. It would be well if more work were done along the lines of Fischler and Kossow, to learn whether their results are significant or accidental or whether any other conclusion is possible. Too much importance must not be attached to perfusion experiments or to the milligrams of acetone formed. It may well be conceded that liver cells are able to form acetone, also that acetone formation is more active in depancreatized and phloridzinized than in normal animals. But the negative experiments with muscle and other organs do not prove that they are unable to form acetone bodies or that the quantity which they form is small. For example, authors have reported that the liver perfused with glucose forms glycogen, but no one has demonstrated the formation of glycogen when muscles are thus perfused, and it is certain nevertheless that muscles in the living body form much glycogen. The function of the liver is primarily metabolic; perhaps for this reason it gives more positive results on perfusion than other organs in which the metabolic is subsidiary to other functions. At any rate the reason for the close scrutiny of these experiments lies in their disagreement with the chemical views of fat metabolism above mentioned. It would seem that only in the tangled field of diabetes could writers put together such doctrines as the predominant production of acetone bodies in the liver and the chemical views of Magnus-Levy and Knoop, with no consciousness of conflict. If there is anything like the excretion of one molecule of acetone bodies corresponding to each molecule of fatty acid

burned, and if it be claimed that any large proportion of the acetone bodies arises in the liver, it follows either that the liver is burning this same high proportion of the fat, or else that the muscles are burning part of their fat perfectly while the liver is breaking up individual fatty acid molecules into several molecules of acetone bodies. Von Noorden's hypothesis is at least consistent on this point. But if, according to the accepted belief, cells in general attack the fat molecule directly, then acetone bodies are formed where the combustion occurs. In Woodyatt's metaphor, the engine "smokes" with acetone bodies. And since the great preponderance of combustion is in the muscles, it follows that the predominant formation of acetone bodies is in the muscles. The only escape would be in an improbable assumption that the muscles burn fat to a certain point and that hypothetical products are conveyed from them to the liver to be formed into acetone bodies. The proof for the chemical theories is not absolute, but it seems stronger than that for the origin of acetone bodies in the liver. Therefore, the most probable view at present is that the formation of acetone bodies takes place mainly in the muscles and other organs and only to a minor extent in the liver.

It is impossible in the present space to review the literature of acidosis or even the literature of fat-feeding, which more directly concerns the present topic. It is well known that fasting human beings regularly show ketonuria. It is not generally appreciated how widely this phenomenon varies even in supposedly normal persons. Waldvogel and Brugsch observed instances in which fasting produced only trivial acetone excretion. Benedict's fasting man, eliminating approximately 2 to 7 grams of acetone bodies daily, may be considered a fair average. The upper extremes are represented in reports by Von Noorden of excretion of 48 grams in three days of fasting by a girl with gastric ulcer, by Bönniger and Mohr of excretion of over 24 grams in one day by a fasting woman, and by Gerhardt and Schlesinger of 40 grams daily in hysterical vomiting. The available store of body fat is one important factor, and Folin and Denis published a recent illustration of marked acidosis with symptoms in fasting obese women. But it is not certain that this is the sole variable, and only a large statistical study could show whether normal persons of similar nutrition have inherently different susceptibilities to acidosis. Ketonuria likewise results from simple carbohydrate abstinence, and fasting ketonuria is increased by protein-fat diet. Protein is considered antiketogenic in normal persons, the glucose-forming amino-acids prevailing over the others. Evidence that it may give rise to ketonuria has been offered by Rosenbloom and Hurtley for diabetic patients and by Kirk for depancreatized dogs. Such an effect is possible through loss of the carbohydrate portion leaving the ketogenetic portion, through a simple stirring up of metabo-

lism and elimination (just as a submaximal D : N ratio in a fasting depancreatized dog may rise to maximal on feeding), and, in human patients, probably through aggravation of the essential diabetic process. In line with this, a high protein diet is inadvisable for the average patient threatened with coma. Fat constitutes the essential dietary cause of ketonuria in normal persons; for example, Landergren and Forssner thus produced excretion of some 40 grams of β-oxybutyric acid. Attempts have been made to establish the quantity of carbohydrate requisite to prevent acidosis, the figures generally being set at 50 to 150 grams. Geelmuyden found that more, perhaps 200 grams, might be necessary to abolish an existing acidosis, also that the quantity required varies with the quantity of fat in the diet. Zeller worked out a law that for prevention of acidosis one molecule of sugar must burn for each two molecules of fat, which means the ingestion of one part of carbohydrate for four parts of fat. Von Noorden and his followers have emphasized the wide discrepancies between different diabetics as respects the relation between carbohydrate assimilation and acidosis: for example, Mohr's comparison between two patients under similar conditions, one of them excreting less than 1 gram of β-oxybutyric acid and the other over 15 grams, and his records of other patients with abundant ketonuria while assimilating 120 to 150 grams of carbohydrate. But Mohr mentions a similar discrepancy between two non-diabetics, and Forssner excreted 33 grams of β-oxybutyric acid with 40 grams of carbohydrate in his diet. Gigon tabulates the Landergren and Forssner experiments to show that individual idiosyncrasy is as marked among non-diabetics as among diabetics. It is well recognized, as shown in experiments of Reich quoted by Rosenfeld, that an initial ketonuria generally diminishes on continuance of the same diet. This behavior of normal persons is usually shown by diabetics who do well, and Mohr states that obese persons respond similarly. Folin and Denis observed that repeated fasts in obese subjects produce, so to speak, an "immunity" against acidosis, and the same has been noticed a number of times in our diabetic patients. A minority of diabetics develop serious acidosis on fasting, but when a short period of suitable diet, even protein-fat diet, is interposed no case has yet been encountered in which a second fast was not well borne. On the other hand the Landergren-Forssner experiments give no indication of any such "immunity" to excessive fat diet. The great lack is of normal data. The Eskimos are much talked about but have never been studied. It is really unknown to what extent the normal human organism can accommodate itself to fat combustion or what proportion of protein or carbohydrate is the minimum necessary permanently to prevent acidosis. Some interesting acetone and ammonia figures ought soon to become available from severely diabetic patients who are kept free from

glycosuria for long periods on diets low in protein and carbohydrate. The fat tolerance in such patients seems to differ widely. The susceptibility to acidosis may perhaps also be governed partly by variables such as the age or the level of nutrition, whether high or low. Even under identical conditions the attempt to establish a universal rule on this point promises to be fruitless, for the reason that the widespread belief regarding acidosis as governed solely by a supposed ratio between fat and carbohydrate in combustion is incorrect. The existing evidence against it may be summarized as follows: (1) the seemingly constitutional idiosyncrasies manifested by both diabetic and non-diabetic individuals, shown in the literature; (2) the acidosis in certain infections, intoxications, liver necroses, and in the cyclic vomiting and gastro-intestinal crises studied by Howland and Marriott and others in which deficiency of carbohydrate seems an inadequate explanation; (3) the acidosis which Taylor produced in himself by an ash-free diet of seventy-odd grams of protein, 120 grams of fat, and 200 grams of sugar. It is well for those who think of acidosis as necessarily due to lack of carbohydrate to bear in mind this well-authenticated case in which it was produced by lack of salt on a diet adequate in protein, moderate in fat, and liberal in carbohydrate. Rumpf and Joslin's idea of the importance of salts for threatened coma may find an analogy here. The fact that salt starvation has not had this effect in other such experiments perhaps adds to the evidence of personal idiosyncrasy. The experiment might bear repetition in subjects presumably disposed to acidosis, as the obese.

Notwithstanding that fat ingestion has been proved to create or increase ketonuria in both normal persons and diabetics, fat has remained the one unrestricted food in diabetes. Even Forssner saw reasons to justify the prevailing treatment, considering that tolerance for fat is acquired, that its addition to protein then increases ketonuria by only a few grams, and that its use is preferable to undernutrition. Naunyn, von Noorden and all others have agreed that fat should be withdrawn only in the presence of threatened coma. The few writers who have advocated occasional restriction of fat have merely favored limiting it to the caloric requirement of a maintenance diet. The more common practice has been to push fat by all possible devices to the utmost limit of the digestive power, with the idea of building up strength and nutrition. Another support for the fat diet was given in the statement that the heaviest fat feeding only slightly increases the combustion of fat, the surplus being stored. In this connection the question arose why then ketonuria should be increased by fat ingestion, and various authorities inclined to the view that food-fat may somehow behave differently from body fat in metabolism. Murlin and Lusk proved that six hours after taking 75 grams of fat a dog's heat production may be 30 per cent. above the basal.

The protein-sparing power of fat is known to persist in diabetes. Therefore the absolute and relative increase in fat combustion now appears a sufficient explanation of the slight increment of ketonuria following any single fat meal, and the summation of such effects presumably accounts for the results of longer feeding, so that there is at present no evidence of a metabolic distinction between food fat and body fat. The relief of diabetic acidosis by fasting is doubtless due not only to diminished combustion of fat but also to a beneficial effect of undernutrition upon the assimilation of all classes of food. The fact that patients with severe diabetes frequently become almost free from acidosis, under the circumstances which give rise to a very appreciable acidosis in normal or mildly diabetic persons, would not appear so paradoxical if we had adequate information concerning the reactions and accommodations of normal subjects under truly comparable conditions. The diabetics merely demonstrate a reserve power in the human organism which normal persons could doubtless bring forth under an equal stimulus. Typical of the former treatment of diabetes has been the period when the patient was evidently developing this power and becoming able to live on protein-fat diet with little or no ketonuria; then the later period with heavy ketonuria, whether sugar-free on strict diet or glycosuric on mixed diet, and the necessary end in coma. The moral is that the natural or reserve powers of assimilation should be protected in treatment and should not be broken down by overfeeding with fat or any other food. The material for clinical experiments heretofore has comprised either fairly mild cases or severe cases with the usual heavy and fluctuating ketonuria. The tests under these conditions have failed to reveal the insidious and cumulative injury caused by fat. When severe cases are made free from glycosuria and ketonuria, a material is afforded upon which any careful clinician can convince himself of the harm of excess of fat. Washing butter to remove traces of lower fatty acids while overwhelming the system with fat which must necessarily be katabolized into lower acids is one of the absurd practices of past treatment now abandoned. And finally it is to be noted that severe cases kept alive for months or years on low protein and carbohydrate, with glycosuria and acidosis kept up essentially by fat, are the cases that offer the greatest difficulty for successful treatment or for building up a tolerance for any kind of food.

It is important to extend research on acidosis to species other than man. A really satisfactory reproduction of the human condition is one of the greatest needs, for the very sake of the knowledge of how to produce it, and also for the opening up of a subject which always comes when it is made susceptible to animal experimentation. It is also desirable to study this disorder in species which do not so closely imitate man, because in man certain fea-

tures are found quite regularly associated, and are generally conceived as belonging together, and it is valuable to learn whether this association is inevitable, and if not, to take such an opportunity to study the individual factors thus separated. There is no known laboratory animal which reacts precisely like man in this respect. Some apes or monkeys may be expected, according to Baer's findings, to show fasting ketonuria; but the large ones are too scarce and expensive, the smaller ones lack stamina, and it is doubtful if any of them can meet the requirements of appetite and digestion. Other species, as a rule, show ketonuria neither on fasting nor on protein-fat diet. A distinction is generally held between carnivorous and other animals, presumably on the assumption that animals accustomed to carbohydrate will have difficulty in burning fat without it, and on a vague generalization of the observations that dogs and cats are less easily subject to acidosis than man. The first thing learned in studying a variety of species is that this distinction is wholly mythical. There are differences between species but none between classes of animals. Baer observed that herbivora are as immune to fasting ketonuria as the carnivora. He reported ketonuria in a pig on fasting but not on protein-fat diet. A pig which we studied at the Institute proved more resistant to ketonuria than any dog; and persons who may have cherished a secret objection to being classed as the metabolic brothers of the omnivorous pig may be gratified by our experience that no other mammal reacts less like man. On the other hand the typically carnivorous badger shows ketonuria, which in diabetes begins almost simultaneously with the glycosuria. The dog is the best and most human of animals in the laboratory as elsewhere. He talks with his eyes and tail instead of his tongue, and there are some metabolic differences of similar degree. But he has told us so much of what we know about diabetes that it would be important to find a way for him to reveal the one thing on which he has thus far given scanty and unsatisfactory information, namely, diabetic acidosis. There is evidence that the dog stands ready as usual to do his part, and the fault has been with us. Von Noorden and Mohr have tried to make the matter too simple by affirming[2] that if a dog is kept a long time on bread diet so as to accustom him to carbohydrate like man and then changed suddenly to strict meat diet, a heavy ketonuria results. No experiments are cited in support of this assertion, which would seem to be imaginary; at any rate it is untrue, as we have found in a sufficient number of dogs, some of which had lived on carbohydrate for their entire lives. But Neubauer states the observation that very young dogs may show ketonuria on fasting, thus presenting an unusually close similarity to man. Veterinary literature proves that dogs are sus-

[2] Von Noorden, Die Zuckerkrankheit, 1912, p. 137.

ceptible not only to spontaneous diabetes but also to the termination in coma. Fasting phloridzinized dogs show heavy ketonuria, and von Mering, Lusk and others described the limp and semiconscious state which may result. Marriott demonstrated ketonemia in such animals, and we have found high ketonuria and low carbon dioxide in the terminal condition, which therefore seems truly analogous to diabetic coma. But as usual there are differences between phloridzin poisoning and diabetes. According to Baer a phloridzinized dog shows ketonuria only when there is a negative nitrogen balance. Perhaps this is why Geelmuyden found fat to diminish the ketonuria. None of our experiments have dealt with nitrogen balance sheets, but the impression certainly is that phloridzinized dogs show ketonuria on diets moderate in protein and high in fat, and this is strongly in accord with the probabilities. The most important distinction lies in the effect of carbohydrate and protein. Benedict and Osterberg proved that protein feeding causes a fall of 50 to 90 per cent. in the ketonuria even though the D : N ratios showed that all sugar formed from protein was quantitatively excreted. Obviously, protein does not work such a transformation in diabetic patients, and these authors correctly concluded that great caution must be used in interpreting the results of acidosis experiments in phloridzinized animals. The great majority of totally depancreatized dogs show only slight ketonuria and no coma or other acidosis symptoms. Sass using the Loewy-Zuntz titration method could detect no lowering of alkalinity in their blood. From the large number of depancreatized dogs in the Minkowski clinic Allard was able to report several dying in coma with considerable ketonuria. Kirk notes some similar deaths in his pancreas-fed dogs, also a higher ketonuria when fat was fed along with pancreas. Apparently the lower D : N ratio of the depancreatized dog suffices to explain the less marked acidosis as compared with the fasting phloridzinized dog, especially in view of the large quantities of protein katabolized. The great objection to totally depancreatized and Sandmeyer dogs is their cachexia and defective digestion.

Having dogs with severe diabetes and satisfactory digestive power, and desiring to produce in them if possible a facsimile of clinical acidosis, it is reasonable to proceed by subjecting them to the same conditions as human patients. To the question whether successful results can thus be obtained in dogs, the experiments now permit answering yes; that acidosis can be regularly produced in dogs not merely in one way but in three ways, of which gradations and combinations exist, but which are most conveniently described separately, in order to show the complete imitation of the human phenomena.

First we may take the classical treatment of severe diabetes. This has been based upon a too clever caloric conception. The

tendency of the diabetic is to emaciate because of deficient assimilation. The superficially smart idea has been to force up his weight by the trick of crowding calories into the diet to replace those lost in the urine, and of supplying these calories in the form of a food of which the body has only slight ability to relieve itself by excretion, namely, fat. The dog is an ideal subject for such a treatment. On the one hand, by reason of his lower D : N ratio, he loses less sugar than the very severe human cases, and he has a natural high resistance to acidosis; on the other hand, he is able to digest and metabolize far more food per kilogram of body weight than any human being. Therefore, it is an interesting experiment to take a suitable dog, free from cachexia, and see what happens when he is forced either to hold or to gain weight in the presence of severe diabetes. He cannot long hold weight on carbohydrate or protein; the one food for the purpose is fat. It is like the old fancy of the irresistible force meeting the immovable body; and in the present instance either digestion or metabolism, no matter how strong, must break down. Sometimes it is the former. In some dogs, and in any dog if the diet is not carefully adjusted, vomiting, diarrhea, and loss of weight prevent a perfect result. The tendency to digestive disturbances is like that of human patients on similar treatment. If digestion and absorption remain adequate, the breaking down of metabolism is manifested by increasing acidosis. There is repugnance to fat and hunger for carbohydrate as in human patients, but the animal's wishes must be disregarded, as has been done in human cases, and the fat given forcibly if necessary. The highest fat diet is the most quickly toxic, but excessive quantities of fat are not required, and both protein and carbohydrate aid digestion and do not interfere with the result so long as fat is continued. In the long run suet is probably the form of fat best liked and digested. Talcum powder is useful in the diet to control diarrhea. For the size of dogs used, the acidosis diet has sometimes been 150 to 200 grams suet and 200 to 400 grams beef-lung, or 100 to 150 grams suet, 200 grams lung, and 50 to 150 grams bread. Lipemia is present; there is malaise and depression of spirits as in patients with acidosis, and digestive upsets increase. If the animal is well suited for the purpose, if the diet is properly adjusted, and if there is enough day and night watching of all details, it can be shown that dogs thus go into fatal diabetic coma on full mixed diet. Dog 327 was our first and a very typical case. Table IV shows the clinical details of this final period.

Second, we may take the customary treatment of moderate diabetes and illustrate it in dogs. Suppose that suitable operation and overfeeding have produced a condition in which there is marked glycosuria on a kilogram of lung, but sugar-freedom on 800 grams lung, along with a fair state of nutrition and entire absence of

TABLE IV.—DOG 327 (PARTIALLY DEPANCREATIZED).

Date. 1916.	Blood.					Urine.							Weight,† kg.	Diet.	Remarks.
	Plasma sugar, %	Hb. %	CO_2 capacity.	Acetone, qual.	Lipemia, qual.	Volume, c.c.	Acetone, qual.	Total acetone,* mgm.	Total nitrogen, gm.	Ammonia nitrogen, gm.	N : NH_3-N, ratio.	Sugar, gm.			
April 15–16	..	..	..	..	..	922	++++++	91.3	9.082	1.259	7.22	57.33	..	200 gm. lung 200 gm. suet 50 gm. bread	Vomiting and diarrhea frequent during this period.
16–17	0.370	106	22.1	+	++++++	406	++++++	144.8	3.059	0.875	3.50	15.63	..	"	
17–18	0.400	108	29.0	++	++++++	530	+++++	129.9	6.201	0.737	8.40	30.81	19.0	"	
18–19	..	..	..	..	..	1186	+++++	134.0	10.081	1.257	8.00	66.22	18.4	"	Rapidly increasing acidosis symptoms.
19–20	0.400	..	18.5	+++	+++++++	1350	..	489.2	11.475	1.633	7.05	56.70	18.2	"	
20–21	0.314	..	23.3	..	+++++++	1480	..	389.2	10.952	1.717	6.36	51.80	..	"	
21–22	0.500	..	21.4	+++	+++++++	811	..	210.7	4.542	..	..	17.84	16.0	...	Coma.

* Total acetone bodies as acetone.

† Note precipitous fall.

ketonuria. Now place the dog on 600 to 800 grams lung and 100 to 200 grams suet, according to the classical method. There is no glycosuria, weight is gained, and the condition is splendid for weeks and possibly months. The treatment is highly successful. Closer examination shows the presence of hyperglycemia and slight ketonuria, which are usual in the patients of corresponding type. Glycosuria follows, illustrating the spontaneous downward progress which the authorities describe. This is cleared up by a few fast days on the Naunyn plan and the diet is again adjusted; it may now be 400 grams lung and 200 grams suet. The gain in weight continues as before, with hyperglycemia, ketonuria, and subsequent glycosuria. Again the fast days are used and the protein diminished, so that the diet is perhaps 200 grams lung and 200 grams suet. The same cycle is repeated. Now the dog is in splendid condition and spirits, the coat sleek, the appearance such that he might create a good impression out walking in the park, only he has difficulty in remaining sugar-free on even the protein minimum, and the fat may be pushed higher to maintain nutrition against the repeated fast days. If the dog has actually been kept fat, a fasting period about this time may diminish the glycosuria or it may remain high. The previously lively and hungry animal begins to show a curious little mournfulness and complete repugnance to food. A day or two later vomiting of clear mucus begins, and the dog drinks and vomits water. The acetone reaction is heavy; the ferric chloride may be heavy or slight. The alkali reserve of the blood falls low, and the complete picture of patients who go into fatal acidosis on fasting is reproduced. Dogs of the type first described are also subject to this result of fasting if they have been kept fat enough, but fattening is easiest in absence of glycosuria. As in human patients this form of acidosis more resembles the collapse or heart-failure type of Frerichs. The respiration is less typical and consciousness may be retained practically to the end. The outstanding features are the nausea and vomiting and the profound collapse of strength. Table II represents the terminal stage of this condition in dog 280.

Incidentally it may be noted that the cachexia which sometimes causes an apparent suppression of sugar formation in fasting depancreatized dogs is absent in these severely diabetic, partially depancreatized animals, so that their glycosuria and hyperglycemia typically persist almost or quite to the time of death.

The third type of acidosis in dogs is exemplified by diabetic animals kept free from glycosuria by regulated diet or by those in which the amount of pancreatic tissue removed is not quite sufficient to give rise to diabetes. They are free from acidosis on protein diet or on fasting, but on a carbohydrate-free diet high in fat they sooner or later develop marked ketonuria. The protein ration may be governed by the capacity of the stomach. Prob-

ably high protein tends to increase susceptibility to diabetic glycosuria and diminish the tendency to ketonuria. These experiments also may extend over weeks or months, but we have proved upon many dogs that with enough fat in the diet the result is invariable. The qualitative acetone test is heavy but the quantitative output relatively small, generally below 1 gram. An example of this condition is given incidentally in the record of dog 356 (Table V), with potentially severe diabetes. Partially depancreatized non-diabetic dogs on a diet of 150 to 300 grams suet and perhaps an equal amount of lung may thrive in spite of ketonuria for a longer or shorter time. Ketonuria is apt to be slight. But the final outcome appears in one of two forms. One may be digestive failure and consequent loss of weight and strength, with cessation of ketonuria. In the other form the routine measures against vomiting and diarrhea may succeed, but the end comes with a remarkable spastic and ataxic condition, with terminal weakness, convulsions and death. The absence of ketonuria in adult normal dogs on fasting has been confirmed, and has been found true also on high fat diet extending over several months and still continuing. Tests on puppies are only beginning. One young collie suddenly showed a heavy acetone reaction after two weeks of fasting. High fat diet was immediately given. On the third day of this the dog, which was not known to have been pregnant, aborted. This was some two weeks ago. The acetone reaction with low quantitative values has not ceased, but the dog continues to act well. It is not known whether this idiosyncrasy is present because the dog is young, or because of the collie breed, or because of the pregnancy. Normal controls flourish indefinitely, without ketonuria or with only traces, on the same fat-protein diet which causes acidosis in partially depancreatized dogs. A certain number of normal dogs with a sufficient preponderance of fat over protein in the diet develop ataxia and fatal intoxication seemingly identical with that of partially depancreatized dogs, but ketonuria is generally absent or slight. Digestion is upset in them as in the partially depancreatized animals; accordingly, ketonuria cannot be attributed to fatty indigestion. This state of intoxication will require subsequent mention. In partially depancreatized animals the sugar tolerance is diminished. If the ketonuria be interpreted as a diminished fat tolerance, it affords no evidence concerning the unity or plurality of the pancreatic secretion, and in absence of evidence the presumption remains in favor of the former. These experiments are mainly useful as showing that a species which normally has a high resistance to acidosis is made readily susceptible by partial pancreatectomy, and as thus furnishing conclusive proof that the simple balance between fats and other foods does not alone govern ketogenesis but that a specific internal function of the pancreas is at least one of the factors concerned.

TABLE V.—DOG 356 (PARTIALLY DEPANCREATIZED).

Date, 1916.	Blood. Plasma sugar, %	Hb., %	CO_2, capacity.	Acetone, qual.	Total acetone,* mgm. per 100 c.c.	Lipemia, qual.	Urine.‡ Volume, c.c.	Reaction.	Acetone, qual.	Total acetone,† mgm.	Sugar, gm.	Total nitrogen, gm.	Ammonia nitrogen, gm.	N : NH_3-N, ratio.	Weight in kg.	Diet.
Aug.																
24–25	0.200	..	..	..	..	..	269	..	+	..	2.60	7.500	0.820	9.15	11.1	400 gm. suet.
25–26	0.124	106	..	..	..	..	160	..	0	..	+	4.110	0.510	8.07	..	300 gm. suet.
26–27	0.111	..	..	..	..	..	246	..	0	..	0	2.100	1.560	1.35	..	200 gm. suet.
27–28	0.099	..	53.8	..	..	..	192	..	0	..	0	2.670	1.130	2.36	11.4	100 gm. lung; 200 gm. suet.
28–29	..	..	..	..	..	..	352	..	0	..	0	4.100	1.640	2.50	..	Fasting.
29–30	..	..	..	..	..	..	382	..	0	113.1	0	3.570	2.100	1.70	..	100 gm. lung; 100 gm. suet.
30–31	..	..	..	..	..	..	172	..	+	..	0	2.510	1.360	1.84	..	100 gm. lung; 200 gm. suet.
31– 1	..	..	..	..	..	..	140	..	0	..	0	1.580	0.782	2.02	11.4	150 gm. lung; 150 gm. suet.
Sept.																
1– 2	..	..	..	..	..	..	176	..	+	..	0	2.410	0.950	2.54	..	150 gm. lung; 250 gm. suet.
2– 3	..	..	..	..	..	..	160	..	0	..	0	4.320	1.320	3.28	..	150 gm. lung; 250 gm. suet.
3– 4	..	..	..	..	..	..	116	..	+	..	0	1.540	1.020	1.51	..	150 gm. suet.
4– 5	..	..	..	..	..	..	295	..	+	64.9	0	1.593	1.180	1.32	11.75	100 gm. lung; 200 gm. suet.
5– 6	..	..	..	..	..	..	140†	..	++	22.4	0	0.975	0.364	2.66		
6– 7	0.095	90	48.5	0	..	0	357	..	+	86.0	0	3.642	1.175	3.08	11.80	Ditto.
7– 8	..	..	..	..	..	..	258	..	+	49.0	0	2.296	0.413	5.55	..	Ditto.
8– 9	0.083	..	57.9	0	..	0	260	..	+	44.2	0	..	1.000	..	..	Ditto; 8 gm. sod. bicarb.
9–10	..	..	..	..	..	..	842	Alkaline	..	101.0	0	6.399	1.263	5.07	..	Ditto; 5 gm. sod. bicarb.
10–11	0.093	86	67.3	0	..	0	378	Alkaline	0	49.1	0	5.640	0.491	11.50	11.81	Ditto; 10 gm. sod. bicarb.
11–12	..	..	..	..	..	..	380	Alkaline	0	38.0	0	1.642	0.144	11.40	..	Ditto.
12–13	..	..	..	..	..	..	904	Neutral	..	99.5	0	0.814	0.181	4.50	..	Ditto; vomited.
13–14	..	..	..	..	..	..	342	Alkaline	+	68.5	0	2.743	1.180	2.32	..	Ditto.
14–15	0.115	105	67.2	?	..	++++++	170	Alkaline	++++	64.8	0	1.578	0.876	1.80	..	Ditto.
15–16	0.121	93	60.5	+	..	++++	360	Alkaline	++++	84.0	0	3.384	1.332	2.56	..	Ditto.
16–17	0.123	..	58.6	..	..	+	438	Alkaline	++++	53.6	0	3.503	1.051	3.34	..	Ditto.
17–18	0.121	96	64.3	0	..	+	412	Acid	..	30.8	0	0.676	0.144	4.68	12.05	Ditto.
18–19	0.128	..	51.9	0	..	+	220	Alkaline	++++	41.8	0	1.786	0.759	2.36	..	Ditto.
19–20	..	..	..	..	..	..	418	Alkaline	++++	79.7	0	5.643	1.672	3.37	..	Ditto.
20–21	0.149	105	..	+	25.5	+++	664	Alkaline	++++	117.4	0	2.523	1.195	2.10	..	Ditto.
21–22	..	..	..	..	..	..	768	Alkaline	++++++	93.7	0	2.611	1.459	1.79	..	Ditto; vomited.
22–23	..	..	..	..	..	..	670	Acid	..	34.4	0	1.983	0.670	2.95	..	Ditto.
23–24	..	..	..	..	..	..	344	Neutral	..	60.0	0	1.238	0.241	5.12	..	Ditto.
24–25	..	..	..	..	..	..	600	Alkaline	++	..	0	3.108	1.440	2.16	..	Ditto.
25–26	0.179	108	59.5	+++	30.5	++++	870	Acid	++++	..	0	2.302	1.657	1.40	12.20	Ditto.
26–27	..	..	..	..	..	..	790	Alkaline	..	213.3	0	2.465	1.422	1.74	..	Ditto.
27–28	..	98	63.3	0	18.9	+	733	Alkaline	..	43.9	0	1.833	1.393	1.32	..	Ditto.
28–29	0.322	86	61.4	+	..	0	400	Alkaline	..	20.8	0	2.080	0.780	2.66	..	200 gm. lung.
29–30	0.400	..	..	0	31.2	0	565	Alkaline	..	26.2	0	5.763	1.441	4.00	..	
30– 1	0.435	89	..	..	35.7	..	550	Alkaline	+	25.3	5.65	4.554	1.953	2.33	..	}
Oct.																
1– 2	0.250	92	61.4	0	23.2	0	468	Alkaline	+	..	0	2.621	0.772	3.40	..	
2– 3	0.192	95	59.5	0	..	0	636	Alkaline	0	..	0	2.582	0.670	3.85	..	
3– 4	0.175	88	59.5	0	..	0	605	Alkaline	0	..	0	2.009	0.484	4.14	..	} Fasting.
4– 5	0.208	82	59.5	0	..	0	828	Alkaline	0	..	0	2.385	0.621	3.84	..	
5– 6	0.235	88	63.3	+	..	0	842	Acid	0	..	0	2.055	0.505	4.07	..	
6– 7	0.169	76	..	0	..	0	870	..	0	..	0	2.242	0.686	3.25	..	
7– 8	..	..	..	..	..	..	600	Alkaline	0	..	0	..	0.420	..	..	}
Nov.																
3– 4	0.200	..	..	..	..	..	..	..	..	..	..	..	..	..	8.15	200 gm. lung.

‡ Not catheterized. * Total acetone bodies as acetone. † Incomplete specimen.

Of various points perhaps deserving mention, six features of canine acidosis will be chosen for separate consideration. First there are some peculiarities of species seen in the clinical picture. A characteristic of human coma is that the cerebral centers are anesthetized while the respiratory center is stimulated. It may be taken as a general rule that dogs lose consciousness less readily than men, and this applies to their diabetic coma. They begin by showing weakness, drunken gait, and dyspnea especially on slight exertion. The symptoms increase until the animal cannot stand, and the Kussmaul breathing may be typical. The corneal reflex is practically never lost, and even attention to surroundings may be preserved almost to the last. It might appear that the motor centers are selectively intoxicated, until observation shows there is apparent absence of pain in the exposure of bloodvessels or other operations, so that the sensory depression is fully equal to that in human coma, in which a knife-cut frequently provokes some response. The low blood-pressure emphasized by Ehrmann and the soft eyeball noted by Riesman and others have not been tested. Diarrhea sometimes occurs with human coma; in dogs it is invariably present and tinged with dark blood. It occurs whether the coma is produced by feeding or fasting, by diabetes or by phloridzin. It is therefore of metabolic not of digestive origin. At autopsy the liver is typically large and fatty and much fat may be present in the body. There is more or less venous engorgement of the intestine and other viscera, which is the only apparent explanation of the bloody diarrhea, though the bowel contents begin to appear bloody only toward the rectum.

Second, there is the obvious question of the influence of reaction. Toward the end the carbon dioxide capacity of the plasma falls as in human cases, and to a quite similar level. But one advantage of studying the same phenomenon in various species is seen in the fact that in the dog it is easy to maintain normal or supernormal alkalinity of the blood from start to finish, or to raise it suddenly toward the end when it has fallen. In man this is difficult to accomplish even by the highest alkali dosage, but some clinicians have asserted that continuous alkalinity of the urine has failed to save their patients. A few personal observations, and my conception of the acidosis process, have convinced me that this view is essentially correct. Probably the typical dyspnea and coma never occur in man or dog except with acid intoxication. Probably the upholders of the acid intoxication theory of coma are correct on this point, which is, after all, their main contention. Where they seem to be clearly wrong is in the more important matter of extending this idea to mean that a maintenance of reaction would prevent intoxication. Conceivably the secret of the improvement sometimes produced by bicarbonate may lie in an unloading of toxic substances from the cells rather than in a shift-

ing of the alkali-acid equilibrium *per se*. Aside from a possible, very brief, rise in blood-pressure, sodium bicarbonate intravenously or otherwise brings no visible benefit to a dog dying of acidosis. Keeping the alkaline reserve of the plasma continuously normal by means of it or any form or combination of alkaline salts apparently does not prolong the life of a diabetic dog by a single day. The experiments support the conception that acidosis and coma essentially represent an intoxication due to a specific breakdown in metabolism, and that the tendency to alteration of reaction is only an incidental phenomenon.

A third point, closely connected with this, is the ammonia excretion. This was considered the most reliable index of acidosis until the introduction of the tests of alveolar air and blood. Researches beginning with Walter have established that different species vary in their ability to protect themselves against acid intoxication by ammonia formation, and that the quantity of ammonia that can be produced is partly governed by the amount of protein in the diet. Owing particularly to the work of Magnus-Levy and his masterly reviews of the literature, the prevalent tendency is to see in the ammonia solely a reaction to acid poisoning. Therefore, it is well to read the excellent review by Ewing, which gives fairer consideration to other factors possibly concerned. Since the early work of Minkowski, Schütz and others it has seemed that the liver function is one governing factor, and Allard, Rolly and others have upheld the importance of this element in diabetic acidosis. The dog experiments promise to contribute information on this point, but they do not yet permit a conclusion. Normal dogs seem regularly to show low ammonia notwithstanding high fat diet. One of our supposedly normal dogs injured its back while out for exercise, with resultant transitory paraplegia and subsequent polyuria. This dog thrives on either carbohydrate or fat, but shows low ammonia on the former and high ammonia on the latter. Partially depancreatized dogs react to fat diet with such a vigorous ammonia production that the urine is sometimes turned alkaline. Dog 356 (Table V) here gives one example. Alkaline urine on protein-fat diet makes any experienced investigator think of cystitis. To exclude this we now for the most part omit all catheterization and test the animals with a change of food or with alkali. When carbohydrate diet or, as with dog 356, sodium bicarbonate causes a prompt fall in the ammonia and rise in the $N : NH_3$ ratio, cystitis is considered improbable. It is not certain that alkali must necessarily reduce ammonia excretion to normal. The ammonia relations shown in dog 356 and others would seem indicative of reaction or overreaction to acid. Over against these are the relatively low ammonia figures and high ratios in dog 327 (Table IV), notwithstanding the falling alkalinity of the blood and impending death in coma. The essential known difference between the animals is that dog 327

constantly had carbohydrate in the diet. It is possible that the exceptional results are accidental, and as yet we lack the necessary series of experiments to say that they are significant.

The acetone bodies represent a fourth point requiring brief notice. In general, dogs excrete less of them per kilogram of body weight than human patients. It must be remembered that the excretion by human patients is generally not very high except under the influence of alkali therapy, and coma is possible with low ketonuria. The ketonemia seems to be on a par with that of human patients. It is as if the dog's kidney were relatively impermeable to acetone bodies. Also, sodium bicarbonate seems inefficient to sweep them out. A further distinction is that acetone represents a higher proportion of the total acetone bodies than in severe human cases. There is greater similarity to the milder human cases in this regard. What significance it may have in connection with the natural difference between dog and man respecting acidosis is unknown. Miss Wishart conceived the idea of applying the Rothera acetone test to the blood plasma. The test has proved very useful as a routine in the animal work. It has also given dependable results when applied to human patients here and in Dr. Joslin's clinic in Boston. The significant color range varies from the faintest tinge up to the deepest permanganate color. The proteins or other substances in plasma seem to cause no interference. The reaction appears unsuited for exact quantitative application, but it gives a quick, rough idea whether there is dangerous ketonemia or not and whether a quantitative determination is worth while; and as its results do not always run parallel to the urinary reactions it would seem that qualitative tests are more valuable in the plasma than in the urine. The suggestion of Embden and others that acetone is formed chiefly in the urine during or after excretion, from diacetic acid which is the actual circulating substance, appears to be contradicted by the strong acetone and weaker diacetic tests obtained in the plasma. Specific poisoning with acetone bodies has been the principal hypothesis opposed to the acid intoxication theory of acidosis. In denying the latter view we are not necessarily thrown back upon the former. The cause of damage from the metabolic breakdown may or may not be subject to chemical analysis by present known methods. The present work adds to the means for approaching the problem. It is possible that the acetone bodies may some day prove to be an index rather than the cause of the intoxication in acidosis.

A fifth point for mention is the behavior of the kidney, which has recently been studied in human diabetics by McLean and more particularly by Fitz, but which time has not permitted investigating in our animals. Incidental observations show that the usual polyuria of severely diabetic animals is generally diminished

on high fat diet, and oliguria is frequent in spite of high sugar percentages in blood and urine. For some reason thirst is lacking, so the change is not altogether renal. The kidneys are sometimes remarkably impermeable to sugar, after sugar feeding in mild cases but more notably after fat feeding in severe cases, when it is possible to have 0.4 per cent. blood-sugar without glycosuria. An example is furnished by the record of dog 356 (Table V). Neither water nor sodium bicarbonate has been observed to cause edema, but the latter seems not to produce such thirst and diuresis in acidosis animals as in normal ones, and perhaps this is why acetone bodies are not swept out as in the human. Albuminuria is common in acidosis and in simple fat intoxication, but the few observations made have not shown casts. The kidneys of dogs with advanced acidosis have always shown gross and microscopic alterations as far as yet examined, the Armanni vacuolation of certain tubule cells being the most constant. Glycogenic degeneration described by Ehrlich has not been demonstrable by Best's carmine stain. From the absence of edema after nephrectomy and other known facts it is doubtful if dogs are suited for accurate imitation of the renal peculiarities of human diabetics, but it seems probable that excessive fat ingestion has directly or indirectly an injurious effect on the kidneys in both patients and dogs, and that this feature is worthy of more study than we have been able to give it.

The sixth and last point for special mention is the general position of fat in the dietary. The early investigations of the total metabolism founded the conception of the caloric requirement and isodynamic equivalents. A protein minimum has been partially worked out. It has been proved that carbohydrate has a slightly greater sparing action than fat, and particularly by Mendel has been established the importance of individual amino acids for nutrition and growth. The need of salts is known, and the so-called vitamines are a recent discovery. This practically sums up the existing knowledge of nutrition. Against the prevalent belief that a starving organism is benefited by whatever food it can obtain, should be raised the question whether this is ever true of any non-protein food taken in quantities approaching the total caloric requirement each day. The question pertains to the benign carbohydrate. Concerning fat there is no question. Fat unbalanced by adequate quantities of other foods is a poison. It should be recalled that carnivorous animals subsist largely on protein, and though the Eskimo consumes much fat, he also, according to the Krogh report, eats several kilograms of lean meat daily. After a few days of pure fat diet the most voracious cur will starve to death before he will touch it further, and the more strictly carnivorous cat is still less tolerant of fat-rich diet. Against forced feeding the organism protects itself by vomiting, diarrhea, and remarkable cessation of absorption. No form of emulsification or admixture

TABLE VI.—DOG 394 (PARTIALLY DEPANCREATIZED).

Date, 1916.	Blood.‡ Plasma sugar, %	Hb., %	CO_2, capacity.	Total acetone,* mgm. per 100 c.c.	Total fat, plasma, %	Urine.§ Volume, c.c.	Total acetone,* mgm.	Sugar gm.	Total nitrogen, gm.	Ammonia nitrogen, gm.	N : NH_3-N ratio.	D : N ratio.	Weight, kg.	Diet.	Remarks.
Aug.															
6–7	..	..	..	..	..	1731	360.0	48.5	..	..	..	..	..		
7–8	0.285	82	47.1	83.2	..	1302	248.0	43.4	..	..	..	..	..	100 gm. lung; 100 gm. suet;	
8–9	0.270	..	51.0	94.5	0.566	1178	..	60.8	5.30	..	..	..	10.1	100 gm. bread	
9–10	0.250	106	51.0	36.4	..	1900	416.0	80.0	7.40	..	..	..	..		
10–11	0.232	92	..	18.5	0.566	800	130.5	52.0	4.71	0.44	10.71	..	..		
11–12	0.204	..	..	44.8	0.583	630	134.9	23.3	9.50	0.85	11.18	2.45	..		
12–13	..	..	..	..	..	3080†	591.0	19.1	8.65	1.23	7.04	2.21	..	400 gm. lung; 100 gm. suet.	
13–14	0.286	103	32.8	50.1	..	1605	596.0	32.1	11.40	1.61	7.08	2.82			
14–15	0.364	95	40.4	23.4	0.490	704	182.4	22.8	9.10	0.91	10.00	2.50	10.0		
15–16	0.250	95	31.9	80.4	0.290	646	124.8	19.4	8.30	0.84	9.88	2.34			
16–17	0.377	95	31.9	..	2.380	1030	224.9	35.2	9.27	1.40	6.63	..	9.77		
17–18	0.322	..	51.9	41.0	..	1800	195.1	72.0	10.80	1.62	6.68	..	9.70	400 gm. lung; 100 gm. suet;	
18–19	0.365	90	38.5	30.6	1.840	820	288.0	41.0	9.50	0.82	11.58	..	9.80	100 gm. bread	Dark diarrhea.
19–20	..	..	..	..	..	2350†	742.1	47.0	10.10	1.22	8.30	..	..		
20–21	0.276	..	30.9	73.2	0.430	662	119.6	49.2	8.15	0.76	10.72	..	9.76		
21–22	0.263	51	..	41.1	0.765	406	116.7	13.2	..	0.67	..	..	9.50		
22–23	0.295	35	32.8	39.8	0.591	515	226.5	19.5	7.70	0.77	10.00	2.53	9.50		Unwell; entire diet forced.
23–24	..	..	..	..	..	584	163.8	10.7	5.95	0.73	8.15	1.80	9.07		Eats all diet promptly.
24–25	0.214	39	34.7	36.9	0.825	820	316.8	28.7	8.60	0.90	9.55	3.34	9.30	400 gm. lung; 200 gm. suet.	Seriously ill; fed forcibly.
25–26	0.314	26	40.9	29.2	1.090	686	332.2	15.6	6.65	0.82	8.12	2.35	9.16		
26–27	0.237	..	48.1	..	..	680	214.5	14.3	9.85	0.88	11.15	1.45	..		5 gm. sodium bicarbonate.
27–28	0.256	25	60.5	60.3	0.785	390	170.0	7.2	6.00	1.88△	3.19	1.20	8.75		
28–29	0.354	22	54.8	26.2	0.895	675	230.9	14.1	6.75	1.59△	4.25	2.09	8.51	Not fed	Good condition and spirits.

‡ Blood drawn twenty-four hours after feeding. § Catheterized to separate diet periods. * Total acetone bodies as acetone. † Water spilled. △ Cystitis?

with talcum or other inert substances to give consistency resembling that of the normal ration avails against this toxic action. The small proportion of protein contained in cream or suet gives only partial protection. The same result follows more slowly whenever the proportion of fat to protein or carbohydrate in the diet is too high. The craving of diabetic patients for carbohydrate is often illustrated in such dogs. It should be worth while to determine a law of balance for normal animals. Not only has the diabetic animal a specific sensitiveness to fat, but on low protein ration it must be unable to bear as much fat as an animal on high protein. If the danger of glycosuria prevents increasing the protein, intoxication can be avoided by diminishing the fat. The animal is thinner but safer, hungry instead of nauseated. Diabetic patients have been treated on protein requirement and caloric computations and on general experience of what they will endure. One feature of this experience is that the great majority of severely diabetic patients acquire a repugnance to the prescribed diet and refuse to endure it. By will-power they sometimes endure it for a time. Raulston and Woodyatt's patient adhered for nearly three weeks to a diet of three eggs and 800 c.c. of 16 per cent. cream daily. They employed this as a temporary measure, but such low protein, full calory diets have been the ideal of the best workers under the Naunyn method. The fact is that such a diet will send a diabetic dog into coma, and it is questionable how long normal dogs could tolerate it. It thus appears that patients were right in much of their conduct, and their stealing of carbohydrate was not entirely due to original sin but was rather prompted by physiological necessity. They live in fair comfort on moderate protein and little or no carbohydrate as long as the fat is kept suitably low. They behave much more rationally toward simple hunger for all classes of foods than they did toward the former excessive craving for carbohydrate. Lack of self-control still claims many victims, but the proportion of patients willing to follow diet faithfully has been increased by reason of the more natural balance of foods in the diet.

III. Influence on Carbohydrate Utilization.

The third phase of the role of fat in diabetes to be considered now is its influence on carbohydrate utilization, on hyperglycemia and glycosuria.

The literature on this subject is scanty. A small number of writers believe it probable that sugar is formed from fat. A somewhat greater number, including Magnus-Levy, admit the possibility. The great majority recognize the occurrence of such a process in plants, but find no evidence of it in animals. Attempts have been made to demonstrate it in animal experiments, but these have failed so completely that they are not worth reviewing;

whereas, on the other hand, the non-increase of sugar after fat feeding, the dextrose-nitrogen ratio, and the respiratory quotient, as found by Lusk and others, offer seemingly conclusive proof of the absence of such a transformation in the intense sugar-hunger of phloridzin-poisoning. Although Donkin insisted on skim milk for his milk cure, and that cream spoiled it, the first to assert that fat increases diabetic glycosuria was Lichtheim, whose perfectly correct statement is mentioned with disapproval by Weintraud. Weintraud argued that even if fat should in certain cases cause the excretion of a few grams of extra sugar, the food value of the fat is far greater than this, so there is clear benefit. This has remained the position of the Naunyn school. Lenné, von Noorden and others, who hold extreme views of conversion of fat into sugar, nevertheless use fat to make up a full caloric ration. Von Noorden confesses to prescribing fat perhaps more liberally than anybody else. He and Falta and other pupils mention occasional so-called "fat-sensitive" patients whose glycosuria is increased by fat feeding; but this effect is said to follow only the overnutrition produced by excessive fat ingestion, and fat in the quantities practically employed is held not to increase glycosuria, because if it were withheld its place in metabolism would supposedly be filled by body-fat. I have reviewed elsewhere reports of dextrose-nitrogen ratios supposedly proving sugar formation from fat in diabetic patients, but actually proving they were not adequately watched; also the other observations from Griesinger down to Benedict and Joslin and Du Bois demonstrating that no higher dextrose-nitrogen ratios than Lusk's 3.65 value are found in even the severest clinical diabetes, and the respiratory quotients further assure the non-formation of sugar from fat. In view of the general acceptance of these facts it is natural that the possibility of increase of glycosuria from fat feeding should be generally ignored. If an occasional voice asserts from time to time that fat increases glycosuria, the protest is directed only against fat rations considered excessive, and only the most slight and transitory undernutrition has been countenanced by such authors.

It is likewise natural that the glycosuria attributed to fat should be small and that the so-called sensitiveness should be apparent in relatively few cases. The effect of fat was above characterized as insidious and cumulative, even with respect to the acetone bodies which are formed from fat; and at least an equally occult influence should be anticipated with respect to sugar, which seemingly is not formed directly from the fat itself. Its action, though not absent in mild cases, is necessarily difficult to demonstrate. The heavy and variable glycosuria of average severe cases and the already maximal output in the extreme cases hopelessly mask the effect of fat, which therefore is only demonstrable rather doubtfully in an intermediate group. Once more the severe cases freed from glyco-

suria and acidosis afford the best clinical experimental material. Dr. Fitz has been performing some experiments of this type, with unusually complete laboratory observations. One of his protocols is here reproduced (Table VII). The patient, who developed diabetes at the age of fifteen, is now nineteen, and has been under treatment at the Institute for two years. She represents one of the cases in which tolerance is built up very slowly and with difficulty, and on account of tenement environment she loses in a few weeks at home as much as is gained in months at the hospital. Her general condition and power of assimilation are therefore known by long experience. The record begins with high blood-sugar produced by a slightly excessive previous diet. The diet throughout contained a fixed quantity of thrice-boiled vegetables, but no other possible source of carbohydrate. The procedure consisted in keeping the protein intake constant and increasing the fat by about 5 grams daily. The peculiarities concerning chlorides and other features will be discussed by Dr. Fitz elsewhere. The ketone and ammonia excretion increased moderately. The blood sugar first fell, then rose, as the fat was increased. The patient felt better on the higher fat. Such well-being is transitory. Glycosuria appeared in traces and increased to 21 grams. High glycosuria and acidosis can be produced by continuing such an experiment, but safety required checking the injury here by a fast day. It is feasible in selected cases to show that the symptoms subside on simple omission or reduction of fat. This patient is an example of those who can demonstrably live in fair comfort and nutrition for at least several years on low diet almost or absolutely free from carbohydrate, but who would die rather promptly if the traditional building-up process with fat were attempted.

The earliest experiments showing the benefits of continued reduced nutritional level in diabetes were performed on dogs. Notwithstanding the evident clinical results in severe cases there remain physicians who, conceding that such methods may be useful for such cases, find in their experience that patients feel best on liberal nutrition, and see no harm in allowing plenty of fat in the cases in which no immediate injury is perceptible. Also, there are other clinicians who hold that alleged radical differences between diabetic patients prevent drawing general conclusions or treating according to a unified broad conception, and who emphasize spontaneous fluctuations due to infections or other causes, and who try to draw distinctions between the properties of various kinds of fats, and who maintain the comfortable interpretation that bad results under their methods are due to a progressive downward tendency inherent in the condition itself. By choosing the severest cases obtainable and including the poor and ignorant we have made a high death-rate inevitable. Furthermore, our own management has not been perfect, and we have sometimes given too

TABLE VII.—PATIENT B. D. P.†

Date. 1916.	Blood.					Urine.							Weight, kg.	Diet.△			
	Urea nitrogen, mgm. per 100 c.c.	Plasma acetone,* mgm. per 100 c.c.	Plasma chloride, %	Sugar, %	Plasma. CO_2 capacity.	Volume, c.c.	Total nitrogen, gm.‡	Ammonia nitrogen, gm.	N : NH_3-N ratio.	Acetone,* gm.	Chloride, gm.	Sugar, gm.		Protein, gm.	Fat, gm.	Calories.	NaCl, gm.
Sept. 29–30	..	25	0.594	0.204	63.0	4150	4.31	0.54	7.96	1.67	12.85	Trace	37.8	7.4	13.5	150	10
30– 1	..	..	..	..	..	3235	7.14	0.94	7.60	2.56	6.95	Neg.	36.4	33.0	34.0	450	10
Oct. 1– 2	..	..	..	..	..	3380	8.00	0.98	8.16	2.72	3.89	"	36.1	40.0	47.0	605	10
2– 3	..	33	0.606	0.172	65.4	3560	8.00	1.00	8.00	2.43	8.20	"	36.1	40.0	52.0	650	10
3– 4	..	..	..	..	..	3765	9.08	0.94	9.65	1.85	10.00	"	36.1	40.0	57.5	700	10
4– 5	6.9	25	0.593	0.143	66.3	3970	8.65	0.95	9.10	2.01	13.30	"	36.1	40.0	63.5	750	10
5– 6	..	..	..	..	..	3995	7.75	1.00	7.75	2.62	11.80	"	36.0	40.0	68.5	800	10
6– 7	..	24	0.588	0.192	67.4	3360	8.30	1.44	5.76	..	11.30	..	35.6	40.0	73.5	850	10
7– 8	..	..	..	..	..	3595	9.67	0.93	10.40	2.24	7.74	"	35.9	40.0	80.0	900	10
8– 9	..	..	..	..	..	3745	10.70	1.05	10.20	1.63	11.60	"	35.8	40.0	85.1	955	10
9–10	7.0	26	..	0.204	63.0	3555	9.70	0.89	10.90	1.48	11.90	"	35.9	40.0	90.0	1000	10
10–11	..	..	..	..	..	3835	10.25	0.84	12.20	0.96	12.45	"	35.8	40.0	95.0	1050	10
11–12	..	24	0.582	0.182	68.8	3530	8.26	0.84	9.85	1.35	11.12	"	35.5	40.0	100.0	1100	10
12–13	..	..	..	..	..	3290	9.71	0.95	10.21	1.64	9.37	Traces	35.6	40.0	105.0	1150	10
13–14	..	25	0.581	0.200	65.9	3270	7.64	1.18	6.50	2.50	8.82	"	35.5	40.0	110.0	1200	10
14–15	..	..	..	..	..	3465	10.60	1.18	9.00	3.46	10.39	"	35.6	40.0	115.0	1250	10
15–16	..	28	0.588	0.176	61.2	3120	12.25	1.34	9.15	4.40	8.26	1.85	35.4	40.0	120.0	1300	10
16–17	9.9	..	..	..	..	3140	12.20	1.48	8.25	2.86	10.98	21.32	35.6	40.0	120.0	1300	10
17–18	..	..	..	..	..	3330	10.20	1.63	6.25	4.16	8.66	13.32	35.7	40.0	120.0	1300	10
18	8.4	30	0.587	0.221	59.8	..	..	..	..	..	..	..	..	..	Fasting		

† Entire experiment by Dr. Fitz. * Total acetone bodies as acetone. ‡ Note increased nitrogen output as fat is increased.
△ 300 gm. thrice-boiled vegetables daily not reckoned; also 300 c.c. soup daily, containing 1.5 gm. N., not included in the protein figures.

high diets and committed other mistakes. This record might be pointed to in support of the allegation that while fasting is good for coma, and has in fact been employed by others previously, the end result is the same anyhow, and in deciding between coma and starvation it is better to choose the former and keep the patients as comfortable as possible. In defense we might point to the very high proportion of these patients apparently saved and improving and enjoying even comfort and usefulness in cases and to an extent apparently impossible under any former methods. Certainly the experience of the great majority of specialists and general practitioners has declared favorably for the benefits of the new plan, and it would not be possible for a treatment to receive a more cordial reception by the medical profession. But both the permanent establishment of the practical treatment on a basis not shaken by every wind of doctrine, and the full determination of the theoretical and scientific significance of the changes thus produced in the diabetic condition, require a clear demonstration of the principles at issue in animal experiments, in which all extraneous and accidental factors can be excluded, and facts concerning the role of fat in relation to diabetic glycosuria and carbohydrate metabolism can be proved by methods beyond the scope of the personal equation.

The first step in such an investigation is to define the potentialities of the experimental material. The material consists of dogs or other animals with injury of assimilation produced by a surgical resection. They are seemingly free from variations due to heredity or the innate tendencies ascribed to human patients. Their special peculiarities and possibilities must be learned. Glycosuria is more liable to cease spontaneously in cats than in dogs, apparently owing to a slower tendency to degeneration and a greater power of recovery in their exhausted islets. Thiroloix and Jacob first announced that mildly diabetic dogs may be sent into the severe fatal form by carbohydrate overfeeding, like human patients, but they gave no description of controls, and their observations were apparently not long enough to reveal the final fate of the dogs not fed on carbohydrate. On first coming to the Rockefeller Institute over three years ago, I set apart some of the first dogs for prolonged experiments covering this point. Some were to be subjected to successive removal of small pancreatic fragments for microscopic and other purposes. Others after one initial operation were merely kept on certain diets. Shorter tests under a year in length were performed on other dogs and other species. No animals succumbed to operation, but a number to the environment. The finished series is not as perfect as planned, but is adequate for decisive results. The proportion of the pancreas which must be removed to produce a given grade of diabetes is fairly constant in a given species, though the rare individual exceptions

are sometimes marked. There are great differences between species, which are independent of the natural sugar tolerance, diet, pancreatic structure, or any other known factors. The general tendency of the pancreas is to hypertrophy after partial ablation, most markedly in young animals, as Homans stated. Extirpation to any point short of producing diabetes causes no tendency to degeneration of the remnant or to downward progress clinically. When the operation is sufficient for mild diabetes, the food tolerance as ascertained after allowing a few weeks for recovery from trauma will generally hold good for a number of months on suitable diet. There is a tendency to some gain in tolerance, but this is usually easy to break down. It is hard to distinguish the true from a false gain in tolerance, characterized by hyperglycemia without glycosuria. Previous authors have reported this phenomenon after repetitions of adrenalin and in old human diabetes. It is present at a certain stage of overfeeding with sugar, protein, or fat. Part of it may represent renal damage, but a part is probably some reaction connected with the basic nature of diabetes. Within proper limits the animals are very valuable for testing the effects of all sorts of agencies upon the carbohydrate and other assimilation and for distinguishing between diabetes and accidental glycosuria. The downward progress conclusively shown by feeding beyond the tolerance with carbohydrate or protein has been previously outlined. The experiments of feeding within the apparent tolerance have been only recently coming to completion. Dogs with a limited carbohydrate tolerance, when kept long enough at normal weight with carbohydrate below the limit, or on lean meat only, or on mixed lean and fat, finally show a gradual fall in tolerance, and all but one of the animals of this series have died of diabetes. The remaining one, now on protein-fat ration, not only has lost all carbohydrate tolerance but shows active diabetes in the form of constant hyperglycemia and ketonuria. There is no reason why diabetes in an Eskimo should not begin in this way, but the ordinary human diet is such that glycosuria precedes ketonuria. The sudden or slow onset of human diabetes can be imitated in dogs. Several interesting examples of apparent onset after traumatism have occurred, in which it is evident that the trauma merely made active a latent diabetes. This does not exclude the possibility that trauma alone may sometimes cause diabetes in man, any more than the absence of any observed association between diabetes and infection in dogs contradicts the demonstrated facts that infections aggravate human diabetes and that patients have been known to acquire diabetes with an infection and recover completely after the infection. The experiments prove that the ingestion of excessive carbohydrate or protein does not create diabetes but merely hastens its active onset. When the underlying tendency is slight enough, indulgence or avoidance

of dietary excess may be a deciding factor. These, in conjunction with former experiments, make it seem probable that luxus consumption of carbohydrate, nerve-strain, and other controllable influences may affect the incidence of diabetes by bringing out latent diabetic tendencies in a population.

The investigation of the role of fat in relation to glycosuria was undertaken along several lines. The proportion of pancreas which must be removed to induce diabetes in fat and thin[3] dogs cannot be shown to differ beyond the limits of experimental error and individual variation. The essential experiments consisted in depancreatizing dogs so that severe diabetes came on with or without overfeeding, and proving that the glycosuria could be stopped by fasting and kept absent on low diet at subnormal weight, while addition of fat to the diet brought on gain of weight and consequent glycosuria. These were the experiments upon which the undernutrition treatment was founded. The requirement was to make them conclusive. Accidental factors must be excluded, and it must be established whether the downward progress of such dogs is prevented or merely delayed. One possible method is to compare a sufficient series of undernourished dogs with the well-nourished dogs and learn which live longest and how the tolerance behaves. This was done, and in several undernourished animals a gratifying improvement of protein assimilation was observed in contrast to the downward tendency in the controls. But the undernourished animals fell victims to laboratory environment and the attempt had to be repeated. The longest duration was one year, with continued gain in tolerance and strength, which is not without importance. The undernourished state cannot be blamed for causes of death such as rabies, and badly undernourished street curs appear hardy. But in consequence of the accidents none of these experiments were long enough to found a fully decisive comparison. The ideal procedure would be to keep dogs sugar-free for a period on a given diet, then fatten the same dogs by adding only fat to the diet and show that glycosuria ensues, and then remove or diminish the fat and prove that glycosuria ceases and tolerance is raised. These experiments also were long, and were carried to the point where the obese dogs developed glycosuria. These were the first deaths in coma, which were important in opening up the study of acidosis, but highly inconvenient in the present connection through spoiling the chance of showing that the identical animals could be free from diabetes at reduced weight. On the whole the experiments along these lines were of a difficult and disappointing character, such as one would not wish to go through with again. Large pancreas remnants were requisite, in order that the dogs might retain appetite and digestion for fat. Animals must be chosen voracious enough to take hundreds of

[3] "Thin," in the ordinary sense, opposed to obese. Long fasting or extreme undernutrition makes a decided difference.

grams of sugar to break down their tolerance, and later to consume enough fat with restricted protein to become obese, as most dogs will not do. The preparatory period of sugar-freedom and fixing the tolerance was tedious, and after some months the dog might refuse to eat enough for fattening and have to be used for some other purpose. Few laboratories could be expected to repeat such experiments, and the outcome would still be subject to a personal factor. The results of briefer tests were in apparent contradiction to the longer experiments. Addition of fat to a diet causes a distinct depression of blood-sugar during digestion, confirming Jacobsen's findings in human patients. Dog 386 gives an example; Chart VIII shows how the blood-sugar was lower in every instance on protein plus fat than on the same quantity of protein alone. Intravenous glucose injections do not occasion higher glycosuria during alimentary lipemia than during fasting. The reports of Blum and Roubitschek that fat feeding increases adrenalin glycosuria could not be confirmed. The first part of the record of dog 356 (Table V) shows how feeding of only suet diminished the hyperglycemia in an animal with potentially severe diabetes. Even in the severest active diabetes the feeding of pure fat does not increase hyperglycemia or glycosuria. This statement is not altered by the experience that under some circumstances dogs with severe diabetes show a striking increase of blood-sugar after receiving fat; but though this increase may continue for several hours it may begin almost immediately, therefore is obviously not due to anything derived from the fat; and this view was confirmed by finding that an equal amount of kaolin or talcum powder has the same effect. It will be noticed that all the experiments of this order are inimical to the idea of sugar formation directly from fat. In the face of all the uncertainties and contradictions, there was a distinct belief that the long experiments pointed to fat feeding as a potent factor for producing diabetic glycosuria; but the question remained how to make this a positive conclusion instead of a personal impression.

Two changes were introduced. First, a slight increase in the staff permitted following the blood-sugar more satisfactorily. Second, independence of the dogs' caprice was gained by forcible feeding when necessary. The appetite of diabetic patients has never been the guide to their diet. Fat has been given to them disguised by all the arts of cookery, and in addition they have been ordered to drink olive oil and otherwise consume fat beyond their desire. It has not been found possible to fool the instincts and senses of dogs when they begin to revolt at fat, but it is feasible to stuff down a ration exceeding what most dogs will continue to eat voluntarily, and if properly planned it is well digested and absorbed. Since the highest fat gives the quickest results, the experiments are thus compressed into a few weeks or months and are convenient to repeat. The numerous controls show the absence of any similar results in dogs not subjected to the fatten-

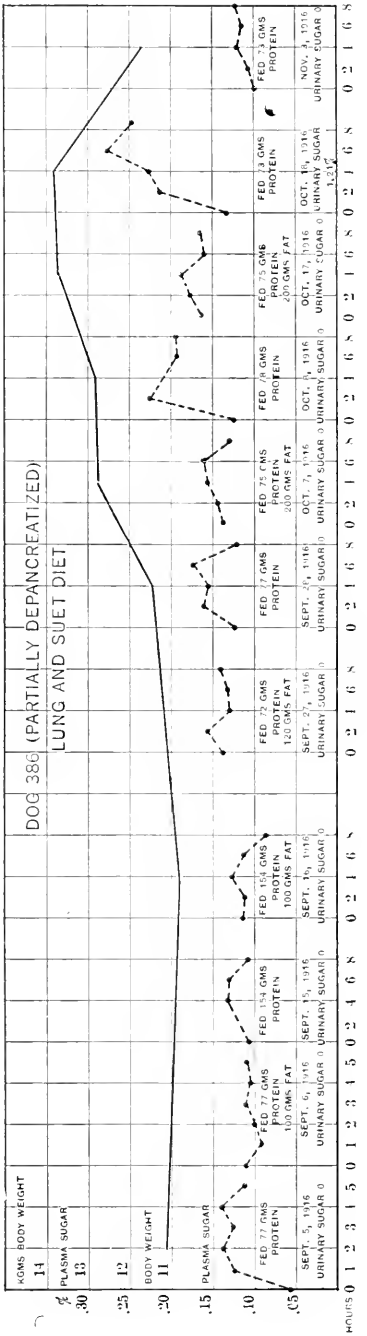
DOG 386 (PARTIALLY DEPANCREATIZED)
LUNG AND SUET DIET
KGMS BODY WEIGHT
PLASMA SUGAR
BODY WEIGHT
PLASMA SUGAR
HOURS
FED 77 GMS PROTEIN
FED 77 GMS PROTEIN 100 GMS FAT
FED 154 GMS PROTEIN
FED 154 GMS PROTEIN 100 GMS FAT
FED 72 GMS PROTEIN 120 GMS FAT
FED 77 GMS PROTEIN
FED 75 GMS PROTEIN 200 GMS FAT
FED 78 GMS PROTEIN
FED 75 GMS PROTEIN 200 GMS FAT
FED 73 GMS PROTEIN
SEPT. 5, 1916
SEPT. 6, 1916
SEPT. 15, 1916
SEPT. 27, 1916
OCT. 7, 1916
OCT. 8, 1916
OCT. 17, 1916
OCT. 18, 1916
NOV. 4, 1916
URINARY SUGAR 0

CHART VIII

ing process. At the same time successful experiments in which greedy dogs ate everything voluntarily show that the forcible feeding is responsible for no difference; and earlier experiences (above described) prove that the same thing happens when the ration is more moderate, only the time required is longer. Two examples of the recent type of experiments are here shown.

Dog 356 (Table V) underwent operation on July 13, which left a remnant of one-eighth to one-ninth of the pancreas. The tolerance was broken down by feeding, so that it was slightly below one kilogram of lung; that is, on feeding this quantity, glycosuria remained absent until the third day, then was 2.85 per cent. It was cleared up by two days of fasting; then on August 21 a diet lower in protein but higher in calories was given, namely, 400 grams lung and 200 grams suet. This dog had been in barely medium condition at her original weight of 15 kilos. The preparatory stage had reduced her to 11 kilos. The greatly undernourished dog ate all the suet eagerly, and tolerated this excessive ration without glycosuria, until on August 25 glycosuria of 2.6 grams appeared, with a fasting blood-sugar of 0.2 per cent. Here lung was omitted, and 400, then 300, then 200 grams of suet fed. Under this huge caloric intake, glycosuria ceased and the blood-sugar rapidly fell, giving no sign of sugar formation from fat. The protein was then cut far below the tolerance, and the fat diminished to what the dog could digest regularly. The normal plasma sugars from September 6 to 11 show that this diet of 150 grams lung and 200 grams suet was well within the tolerance at that time. Weight was steadily gained and the blood-sugar rose in parallel, while ketonuria and lipemia developed. The plasma sugar values on September 28 and 29 without glycosuria illustrate the renal impermeability under these conditions. On September 30 glycosuria developed. The diet at this time was changed to 200 grams lung, being approximately the former protein intake with omission of fat; and it was hoped that the course might thus be changed for the better. But the evil that fat does lives after it. A patient threatened with coma may not necessarily clear up if given a protein ration such as he subsequently may come to tolerate well after fasting; and when the injurious effect of fat has been pushed to this extreme point in diabetic dogs they are narrowly saved by using the same treatment as for human patients, although if the program had been changed earlier the simple omission of fat might suffice to reverse the progress. Accordingly, this dog was promptly fasted and there was prompt cessation of glycosuria and ketonuria. Low diet changed the condition so that the weight on November 3 was only 8.15 kilos, and 200 grams lung without fat caused no glycosuria, though the plasma sugar was 0.2 per cent., showing this ration to be still excessive. This is an example of treatment of severe diabetes by marked

undernutrition. When the dog was four kilos below medium weight the attempt to fatten her up to 3 kilos below the weight precipitated a dangerous diabetic outbreak, even though the gain was accomplished by addition of pure fat and there is no indication that sugar is formed from the fat. Not the kind of food given, but precisely the gain in weight above what the assimilative function is able to carry, is the cause of the breakdown in such dogs and in corresponding human patients. Life is saved by reducing the body mass to what the assimilative power is able to maintain, and if the sparing is adequate, more or less recovery of the function follows in all dogs and in the great majority of human patients. Such an undernourished state as required in this animal, though unpleasant in dog or man, affords the sole means available not only for averting impending death but also for opening the way to a better state. The diabetic has not the choice of a short and merry life versus a long and miserable one. By overtaxing his assimilation he brings on both shortness and misery of existence. These very thin dogs are stronger and happier than the fatter animals with glycosuria and acidosis; and the treatment of fasting and undernutrition for patients has brought not only improvement from the standpoint of laboratory analyses and expectation of life, but also comfort and usefulness and freedom from a multitude of complicating afflictions to a degree never before known.

In other animals as thin as this and with an equally low tolerance, in which the breakdown was produced by carbohydrate or protein, treatment by undernutrition has resulted in steady improvement, as manifested by ability to endure more food and more weight up to a necessary limit. Injury from fat is more lasting and dangerous, presumably because less obvious, so that the harmful process is at work unseen for a considerable time before treatment is applied. This dog 356 finally died in extreme emaciation after a course apparently representing spontaneous downward progress. It furnishes an exact parallel to the type of patients who finally die in spite of treatment, through failing to gain enough assimilative function to support life.

The graphic record of dog 386 (Chart VIII) gives a different example of the same principle. The dog came to the laboratory fat at a weight of 15 kilos, and the operation on April 28 left a remnant of only one-twelfth to one-thirteenth of the pancreas. Thus the tendency to diabetes was made more pronounced than in the preceding dog; but in consequence of more careful diet, for a longer period, the actual assimilation and condition were better. The tolerance was approximately 800 grams lung, which caused slight glycosuria on August 10, when the dog weighed 11.8 kilos, and no glycosuria on September 15, when the weight was about a kilo less. Meanwhile the regular diet was 400 grams lung, which was tolerated for a month without a trace of glycosuria. On September 18 the

diet was changed to 350 grams lung and 150 to 250 grams suet, which was continued except for a few test days for just a month. The animal behaved splendidly, enjoyed the diet throughout, and permitted a flawless experiment. The chart shows that at the outset the only indication of severe diabetes in a dog which seemed so beautifully healthy was the fact that protein feeding caused regularly a rise of blood-sugar like that produced by a large amount of carbohydrate normally. This is an interesting peculiarity of such animals. Not only the 400 grams of lung on September 5 and 6 was well borne, but also the 800 grams on September 15 and 16 caused no hyperglycemia greater than 0.13 per cent., thus proving the assimilation. Then the fat was added to the diet and the weight progressively rose. The chart shows how the fasting values for the plasma sugar were constantly within normal limits on the protein diet, also that where the plasma sugar was determined hourly or two-hourly after feeding the curve after protein plus fat was invariably lower than after the same quantity of protein alone. Nevertheless, as the weight rose the sugar curves also rose. On October 17 the regular protein-fat diet did not suffice for glycosuria, but on the next day the simple omission of the fat sent the plasma sugar so much higher that a glycosuria of 1.21 grams resulted. The attempt to carry this experiment through without fasting was unsuccessful, but on the usual treatment the glycosuria and the ketonuria also present promptly cleared up. On a low diet of protein the weight was brought down to 11.7 kilos, and a test on November 3 showed a fasting plasma-sugar of only 0.1 per cent. which rose only to 0.118 per cent. without glycosuria on the identical protein intake as before. As stated, the operatively produced tendency to diabetes is greater in this dog than in dog 356, but this one represents a case taken before it is so far advanced. This animal can be kept healthy and happy at as high a weight as necessary for either strength or symmetry. Obesity would bring on diabetes irrespective of the kind of food that produced the obesity.

In these and similar experiments one incidental observation is that the blood-sugar is not an infallible criterion for prognosis. It may be within normal limits both before and after meals on a diet which nevertheless is destined to make trouble later. Also, a very high level of blood-sugar may persist for a considerable time after wiser treatment has changed the direction of progress, so that hyperglycemia does not of itself demonstrate a breaking strain of assimilation or preclude improvement. A more broadly important lesson is that the age-long search of chemists for a magic food which diabetics shall assimilate perfectly is as vain as earlier quests of the holy grail or the fountain of youth or the philosopher's stone. What the diabetic organism is unable to assimilate without restriction is not any particular kind of food, but food as

such. From this standpoint all the attempts from the earliest ones with glycerin and lactic acid and levulose down to Rosenfeld's lactone and Grafe's caramel may be judged together and the true reason of their failure appreciated. It is not necessary to conclude that any component of fat is changed into sugar. Although Cremer and Lüthje proved the formation of sugar from glycerin, von Mering first and Lusk more exactly showed that fat feeding does not affect phloridzin glycosuria, and the latter found further that work, which increases fat catabolism, does not alter the D : N ratio, so there is entire lack of evidence that glycerin is split off from fat to form sugar. It may be significant that the experiments and theories of Embden, Neuberg, Dakin, Ringer and Woodyatt, however differing in details, stand in agreement regarding the conception of a merging and equilibrium of chemical products from different sources. It is known that certain substances participating in intermediary metabolism are chemically derivable from either protein, fat, or carbohydrate. Apart from the actual interconversion on a large scale possible between some of these substances, as amino-acids and sugar, it is conceivable that the mere glut of any products is a hindrance to either the anabolism or the katabolism of other products. In such embarrassment of the cells there are certain substances which most readily escape into the blood and urine; but it must not be concluded from this fact that the diabetic fault of assimilation is limited to sugar (as apparently in phloridzin poisoning) or that the intoxication of acidosis is merely due to the acetone bodies. Wells near the seashore rise and fall with the tide, not because any fresh water is derived from the ocean, but because the drainage of the underground streams is blocked in proportion as the tide is high. Such a comparison may explain the production of diabetic glycosuria by fat for those who do not believe in the derivation of sugar from fat. The primarily ketogenetic and secondarily glycosuric action of fat and the primarily glycosuric and secondarily ketogenetic action of carbohydrate are in accord with this speculation. Janney's investigations of proteins cannot show that any amino-acids are harmless, but may indicate which of them are preferable in cases in which the principal immediate tendency is to glycosuria and in others in which the existing tendency is to acidosis.

The most important fact shown by this series of experiments is that the appearance of spontaneous downward progress observed in human patients can be exactly imitated in dogs. It is possible that further factors, notably occasional infections, may be operative in at least some human cases. It is not positive that the undernourished dogs will be able to live indefinitely. But it is conclusively demonstrated that the attempt at high nutrition, even with fat, produces in these dogs an appearance of spontaneous aggravation of condition as striking as anything witnessed in

human patients, and that this result can be prevented at least for periods of years by limiting the total caloric intake and the body mass to correspond to the assimilative function. The experience with diabetic dogs warns unmistakably against efforts to maintain patients on a luxus level of diet or weight. The standard should approach that of Chittenden rather than that of Voit. Restriction of single foods, as carbohydrate or protein, suppresses symptoms temporarily, but lightening the total load upon the weakened assimilative function is the only present means by which it may be hoped actually to halt the diabetic process.

The animal experiments have placed the successful therapeutic results on something more substantial than an empiric basis, independent of opinions or impressions, and no clinical mishaps, whether due to faulty application of the method or to failure of a defective function to recover by rest, can now shake the principles on which this treatment is founded or justify a return to overfeeding with fat and other mistakes of the past.

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ENDOTHELIOMA OF THE RIGHT BRONCHUS REMOVED BY PERORAL BRONCHOSCOPY.[1]

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The patient was referred to the author by Dr. J. P. Harley, of Williamsport, Pa., who stated that there were signs of a localized

[1] Read at the Meeting of the American Laryngological Association, May 10, 1916.

pathology in the right bronchus and right lower lobe which, in his opinion, was not tuberculous and was otherwise so unusual as to demand a diagnostic bronchoscopy. The patient's statement (to Dr. Harley) that he had "a sensation as of a 'ball valve' in the right bronchus shutting off his breath, at times when breathing in, at other times when breathing out, impressed the author with the idea that the patient was a neurasthenic, in view of which a diagnostic bronchoscopy did not seem justifiable. The outcome showed this opinion erroneous. The following is the history:

CASE HISTORY.—Mr. F., aged thirty-five years, occupied as a clerk at a desk and around a factory, had had good health until five years ago. Ill health started with a "heavy cold" lasting one year; then he spat blood. Symptoms were less during summer. Every winter's end and spring, symptoms were worse, starting as "heavy cold" and ending in ill health. Patient refers sensations ("restriction, swelling, compression, wheezing") to his right side. Wheezing audible with mouth open, worse after expectoration. Breathing never seems normal. Has sensation of secretion in bronchi, also sensation of "flapping" at times. Also a sensation as of a ball valve suddenly shutting off sometimes inspiration, at other times expiration. Twice yearly has cycle of the following symptoms in the order given: (1) Cold in head. (2) Tightness in chest. (3) Cough. (4) Slight expectoration. (5) Free expectoration. (6) Bleeding, which formerly amounted to about a fourth of a cupful, and was followed in a few days by expectoration of blood clots. Recently only blood streaks were noticed in expectoration.

He spent two years in a sanatarium for the tuberculous. Discharged because no bacilli could be found in sputum, but cough and wheezing persisted. Roentgen-ray examination and sputum examinations, guinea-pig inoculation, Wassermann and therapeutic luetic tests at a large eastern hospital, were all negative. Diagnosis then made: enlarged bronchial gland. No treatment was beneficial. No sputum test had been made during the last twelve months. Bronchoscopy by someone was negative. Septum deflected by "foul tip" at basball some years previously. Septal operation by Dr. Ritter cured persistent headaches.

Diagnoses of various clinicians prior to coming under observation of Dr. Harley were: tuberculosis, chronic right-sided bronchitis; monolateral (right) asthma; compression stenosis of right bronchus, probably caused by adenopathy. Dr. J. Chalmers Da Costa had made what ultimately proved to be a correct diagnosis of obstruction of the right bronchus.

Report of Sputum Examination by Dr. Ernest W. Willetts. "Very careful repeated examinations for tubercle bacilli both by direct smears and also by antiformin method failed to show them. The sputum contains some small whitish masses of solid matter, which, on examination, showed many large cells of varying shapes. Some

oval, some spindle-form and others polygonal. They are unlike any of the cells ordinarily seen in sputum and are so like cells from a new growth that a diagnosis of tumor is, I believe, justifiable."

Report of Dr. George C. Johnston. First Fluoroscopy. Fibrosis of right lower lobe bronchus. Patient presented symptoms of unilateral asthma on fluoroscopic examination. Left lung and diaphragm normal; parts were normal in size, shape, and position. Right upper lobe normal, but beginning about one inch below bifurcation a trefoil-shaped shadow extending downward was seen. The diaphragm on the right side could not be distinguished. The lower lobe of the lung was replaced by a shadow having exactly the opacity of the liver. It was impossible to state where the liver ended and the lung began. The appearance was that of an unresolved pneumonia. This portion of the lung could not be made to light up on deep respiration or coughing. No motion of the right portion of the diaphragm could be seen nor could its position be located.

Second Fluoroscopy. At a second examination two days later a considerable change had occurred. Some portions of the dense shadow were clear, showing that the lower lobe was occasionally receiving small quantities of air. The diagnosis of atelectasis due to right bronchial obstruction was made, and diagnostic bronchoscopy was strongly urged.

Roentgenographic examination (Fig. 1) showed an opacity of the lower lobe continuous with the hepatic opacity, the dome of the diaphragm on the right side being indistinguishable.

Physical Examination by Dr. John W. Boyce. At the date of the first examination there was some contraction of the right side and a slight impairment of percussion note, both of them corresponding to extreme expiration as though the air could not get in. Vesicular sound was suppressed and replaced by large wheezing rales. There was evidently obstruction in the right main bronchus, affecting inspiration more than expiration at this particular time. There was some impairment of supracardiac resonance and also an increased area of conduction of whispered voice at the back; but both of these signs (suggestive of bronchial adenopathy) extended rather to the left than to the right.

Aneurysm or other mediastinal tumor having been excluded, we have to consider the possibility of a single lymphatic gland making pressure on the bronchus. This diagnosis has been suggested by an expert clinician. Against it is the fact that there is no evidence of bronchial adenopathy. Nor can we conceive how pressure from without could exert a valvular effect, occasionally reversing the direction of the valvular action. The same considerations apply to organic stricture almost hermetically tight, large caliber strictures being latent as regards dyspnea. The long duration of attacks seemed to exclude spasmodic stricture.

It remained then for us to consider transparent foreign body and pedunculated intrabronchial growth. Dr. Jackson theoretically excluded the former on the ground that a movable foreign body in the open bronchus would certainly produce purulent sputum and foul breath in less than five years' time. This narrowed down the diagnosis to a movable intrabronchial tumor. The only objection to this diagnosis is, as Dr. George C. Johnston expressed it, that it "explained every item of the history and physical examination too nicely." Clinical diagnoses and pathological conditions rarely fit so precisely.

Bronchoscopy. Under local anesthesia I passed a 9 mm. bronchoscope. A moderate amount of secretion was encountered coming upward from the right bronchus. When this was cleared away and the bronchoscope was inserted into the right bronchus to the point where the image shown at B, in Fig. 2, should normally appear the tumor (A) came into view. The tumor filled a dilatation of the right stem bronchus and sprang from the right bronchial wall, just above the orifice of the middle-lobe bronchus.

The history of five years' duration, the smooth shining surface, slightly nodular shape, and the fact of the tumor having made for itself a dilatation of the bronchus, lead the author, in consultation with Dr. Ellen J. Patterson, to conclude that the growth was benign, probably fibromatous, and to advise immediate removal without withdrawal of the bronchoscope. The patient gave his consent by a slight nod, and the growth was extirpated in a few minutes by successive nips of the bronchoscopic tissue forceps. The bleeding was not severe; possibly as much as two ounces of blood were expectorated. The temperature rose to 102.2° F., the pulse to 98, the respirations to 30. All came to normal in about one week. Expectoration of blood-stained pus gradually diminished until it disappeared at the end of about four weeks. The patient has had uninterrupted good health until the present time—nine months. The present condition of the patient is thus reported by Dr. Harley:

"In replying to you regarding Mr. F's. condition, I wish to say the word "fine" does not half express his good condition. He has gained twenty-six pounds in weight; has enjoyed the best health this winter for six years, not having the slightest bronchial affection all winter; just feeling at the "top of the heap" ever since his operation. I feel sure he is grateful to you every day of his life for this most remarkable cure."

Report of Histological Examination of Tumor by Dr. Ernest W. Willetts:

"Frozen sections show a very cellular structure which presents the general appearances of an endothelial growth, although in some areas there are appearances that indicate epithelial origin. Nuclear changes are not marked, but the growth is so cellular and infiltrates

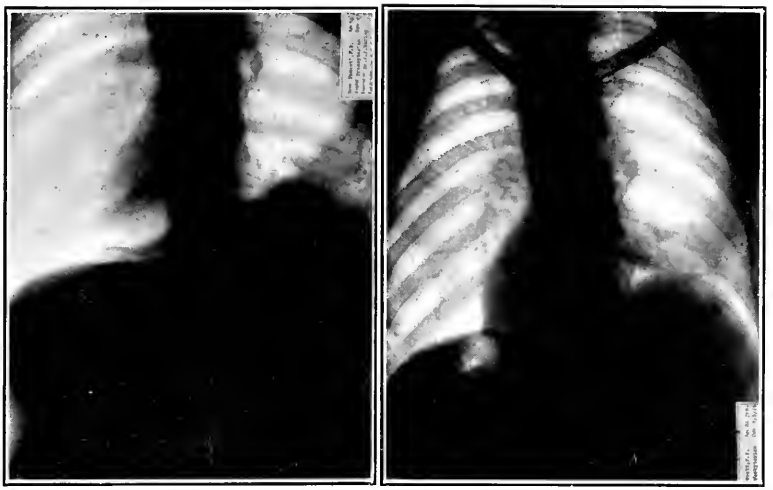

FIG. 1.—Roentgenogram showing (on left) opacity of lower lobe of right lung, due to obstruction of right bronchus by tumor shown in Fig. 2. The right-hand side of illustration shows roentgenogram taken after peroral bronchoscopic removal of tumor.

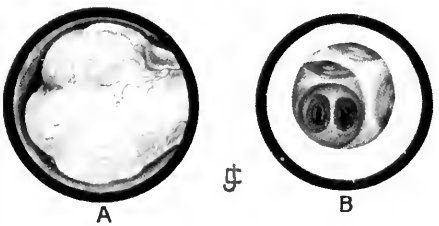

FIG. 2.—Endobronchial obstructing endothelial tumor in a man, aged thirty-five years, who complained of coughing, wheezing, and "a sensation as of a ball valve shutting off his breath, sometimes on inspiration and at other times on expiration. *B*, bronchoscopic view down right main bronchus. *A*, tumor presenting itself in its self-made bronchial enlargement, when the bronchoscopic tube-mouth reached the location at which the view *B*, should appear. Tumor removed with forceps through a bronchoscope passed through the mouth. Patient free from symptoms at end of three weeks and remained perfectly well a year and a half later.

the supporting tissues in such a way as to suggest malignancy. Later examination of paraffin sections only confirms original opinion."

Remarks. In discussing the paper of Dr. J. M. Ingersol at the meeting of the American Laryngological Association in 1914, I spoke against the attempt at bronchoscopic removal of endotracheal malignancy; and such being my conviction, I would not have removed the endobronchial growth in the present case had I not felt at the time that it was benign. The present condition of the patient, however, indicates that Dr. Ingersol's position as to the possibilities of bronchoscopic removal may be nearer right than my own, though he referred only to tracheal growths, while my case was bronchial. It would not be right, however, on the basis of this unique case, to sanction the indiscriminate bronchoscopic attack of pulmonary malignancy. It seems scarcely possible, bronchoscopically, to remove malignancy completely in many instances; and we all know only too well the results of partial removal elsewhere. So far as the present case is to be taken for guidance, it can apply only to a sharply circumscribed non-ulcerated tumor of very slow growth. Moreover, it may be that the tumor was one of those that is histologically malignant and clinically benign. Or, it may be that it was of a very low degree of malignancy, for we know that there are degrees of malignancy or of individual vulnerability; and, as stated by Wright, it is not possible to make a prognosis from the histological examination of a growth. Finally, we know that recurrence is yet possible. In view, however, of the very great rarity of the case and the necessity for us all to be alert to the possibilities of diagnostic bronchoscopy, longer delay in making this report seemed inadvisable, especially in view of the fact that the present condition of the patient and his months of perfect health fully justified the relatively minor operation under local anesthesia, even if the growth ultimately recurs.[2]

Conclusions. 1. Diagnostic bronchoscopy is indicated in cases of monolateral "asthma," bronchitis, bronchial obstruction, and in cases of tuberculosis where persistent search fails to show tubercle bacilli.

2. Peroral bronchoscopic removal of an endobronchial tumor is feasible under local anesthesia.

3. General anesthesia might have permitted clotting of blood in the lower bronchi before bechic expulsion, involving septic risk.

4. Peroral bronchoscopic removal may be justifiable in a malignant endobronchial growth if small, circumscribed, and not ulcerated.

5. As this is the only recorded case of apparent cure of an endothelial endobronchial tumor by peroral bronchoscopy, and only the second endoscopic removal of any form of malignant growth from a bronchus, it would be unwise to make too many or too sweeping deductions.

[2] One and one-half years have now elapsed and the patient is in perfect health, without expectoration or any other symptom.

"SPELTER CHILLS."[1]

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and
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(From the Medical Division of the Philadelphia General Hospital.)

In recent years the results obtained from the study of occupational diseases has been most gratifying. Such a study not only often aids in arriving at an otherwise difficult diagnosis, but as a part of industrial hygiene it has become of great importance in the prevention of those ills that are the result of occupation.

With this in mind a systematic study of occupational diseases is being made in the medical division of the Philadelphia General Hospital, and the affection about to be described is one of a number of interesting conditions revealed by this study.

"Spelter chills" is the name given to a condition heretofore but briefly described under such varying terms as brass-founders' ague, brass chills, zinc chills, smelter shakes, das Giesfieber or Staubfieber, and fièvre des fondeurs. We believe the condition results from the inhalation and ingestion of the fumes and flakes of zinc oxide arising from the melting and volatilizing of spelter, which is the commercial name for zinc in its impure state. Spelter chills we found to be the name popularly employed among the local workmen.

The chills occur in brass foundries, in zinc smelters, and in places where zinc is poured. The majority of instances are found in places where yellow brass is manufactured, a process in which a large percentage of zinc is used. The chills do not occur in those engaged in processes in which the zinc is not volatilized. Lehman produced it artificially in a workman by burning zinc. Some investigators have suspected copper as the cause of the chills. This seems unlikely in view of the fact that in the manufacture of red brass, which contains a large percentage of copper and a small percentage of zinc, the chills occur less frequently than in the manufacture of yellow brass, which contains a greater percentage of zinc than of copper. In brass workers employed in finishing or polishing of brass, though they inhale quantities of copper-laden dust, as is shown by the excretion of copper in the perspiration imparting a greenish tinge to the skin, hair, and underclothes, the chills never occur. Lead as a contributory cause may be considered a negligible factor.

A brief description of the process which exposes the workers to

[1] Read before the Section on General Medicine of the College of Physicians of Philadelphia, March 27, 1916.

this ailment may be of interest: Zinc is obtained from its ores, zinc sulphide or zinc blende and zinc carbonate or calamine. Brass is ordinarily of two varieties, red and yellow. The red brass, the better quality, is made up of from two to four parts copper and one part zinc. The yellow brass is made up, roughly, of three parts copper and two parts zinc. The relative proportions of zinc and copper thus determine the quality of the brass.

Brass is manufactured by either the direct or the indirect process, the latter being the safer, though the former is probably in more common use. In the direct process the metals are all fused together at the same time. In the indirect they are fused one after another, the order depending upon the relative fusibility and volatility. The metals are melted in a large crucible, which is first heated to avoid breaking. Into the crucibe is put, first, a mixture of scrap brass or grain copper; rarely are the pure copper and zinc directly mixed in their definite proportions. After the material is melted down the proper amount of copper or zinc is added to secure the desired composition. It requires 2000° F. to melt copper and 770° F. to melt zinc. Hence the necessity of adding the zinc last. Zinc is readily volatile above 770° F., and for this reason must be well submerged beneath the surface of the melted copper. The mixture is then poured into molds. Though the process up to this point exposes the workmen in some degree to the metallic fumes the pouring is probably the source of greatest danger. As the metal is being poured the atmosphere becomes laden with intensely irritating whitish fumes and fine flaky deposits of zinc oxide or "zinc snow," as it is called. Sir Thomas Oliver gives the following analysis of this "zinc snow":

Moisture	9.64
Organic matter	39.42
Silicious residue	9.14
Oxide of zinc	28.82
Oxide of iron	2.78
Copper	1.71
Other matter	8.49
	100.00

Another analysis gives 44.9 per cent. zinc.

It is this volatilized zinc or "spelter" impregnating the atmosphere breathed by the workmen that we think is the cause of the "spelter chills." As to their ultimate cause we are not prepared to speak. Lehman believes the symptoms are due to an auto-intoxication from absorption of dead epithelial cells lining the respiratory tract, the cells being destroyed by the inhalation of zinc oxide fumes. Rambouse says that neither pure copper nor pure zinc gives rise to poisoning, yet the pouring of brass, an alloy of zinc and copper, sets up a peculiar train of symptoms. The question of infection seems doubtful. It is probably an acute intoxication.

Thackrah in England, in 1830, recognized a definite train of symptoms arising from the inhalation of volatilized zinc, but makes no reference to the chills. Greenhow in England, in 1845, described a condition "similar to an intermittent fever of an irregular type." Blaudet and Greenhow were also aware of a form of poisoning observed in brass pourers. The chills themselves seem to have been first observed by Schwitzer, in Germany, in 1862. The observations of Siegel made in Wurttemberg in 1905 are, however, the most valuable on the subject. Rarely has the condition claimed the attention of American writers, a few reports of individual cases only having been made in Chicago, in 1904, by Drs. Ungre and Savin and by Dr. S. R. Pietrowiecz. Dr. Kober comments on it in his report to the House Commission. Dr. Hayhurst in his "Report on the Investigation of the Brass Manufacturing Industry in Chicago" contributes the most elaborate American report.

Conditions Predisposing to Chills.—Respiratory and circulatory disturbances favor a more sudden and severe onset of the chills. Minors and women and those unaccustomed to the work are more susceptible than others. Alcoholism, anemia, malnutrition, and impaired renal function likewise constitute predisposing causes.

Characteristic of the chills is their tendency to attack the workmen every Monday. This may perhaps be due to the free indulgence in alcohol over the week end. The chills occur most frequently in winter, this undoubtedly being due to the greater accumulation of the fumes in the workshop owing to the windows not being open. Their frequency is further increased on damp, cloudy days on accountof the heavy atmospheric conditions and consequent difficulty in clearing the room of the fumes.

Description of the Attack.—The chill may begin while the man is at his work in the latter part of the afternoon and after the second pouring, but more often it begins soon after leaving the shop or in the early evening. (This we think is due to a diminished activity of the sweat glands after leaving the overheated shop.) Free perspiration, by favoring an excretion of zinc, not only aids in aborting the chill but noticeably diminishes the intensity and duration of an attack. For this reason the men resort to hot drinks, the most efficacious, one of our patients told us, being hot milk with red pepper. For the same reason the men wrap themselves in blankets.

The first thing complained of is a creepy, chilly sensation up and down the spine which gradually extends throughout the entire body. It may continue as a mere chilliness, but more often develops into a genuine rigor which lasts for from one-half hour to an hour or even from two to three hours. At its height, cramps and pains in the limbs are apt to occur; abdominal pain is infrequent, except as it may follow the ingestion of cold drinks. The pulse is increased in frequency and there is a slight elevation of temperature. Preceding the chill there is a dry, scratchy sensation in the throat, a sticking, pricking feeling

in the tongue, oppression in the chest, and an irritating cough, usually unproductive. Actual dyspnea is rare. There is a feeling of prostration and of nausea which frequently eventuates in severe vomiting. Diarrhea is common; indeed, the men at all times have a tendency to diarrhea, constipation being rare among brass molders. As the attack subsides the patient, quite exhausted, breaks out into copious perspiration and soon falls into a deep sleep. A temporary loathing for food and an unpleasant metallic taste in the mouth are present on awakening and last a little while.

One of us exposed himself for two afternoons to the fumes and flakes of zinc oxide during the melting and pouring process. In a few minutes the above-mentioned irritative condition in the throat and chest, with coughing, was experienced. Headache also developed, and later a slight diarrhea. No chilliness, however, was felt.

The attacks do not often incapacitate the workers. For this reason, and also because the men accept the "chills" as a matter of course and of no moment, the physician rarely has the opportunity of witnessing an attack. Great numbers of these workmen, it is reported, visit the out-patient department of the Birmingham Hospitals, but always for respiratory and digestive disturbances.

It is doubtful if single attacks of this affection are of any importance, but repeated again and again, as they usually are, sometimes for many years, they undoubtedly produce far-reaching effects in the human economy.

Among the chronic manifestations of the intoxication, those pertaining to the pulmonary system are the most serious. Brass-founders are especially subject to bronchitis and phthisis, and frequently succumb to pneumonia. A very high death-rate from lung diseases is recorded among the Berlin founders.

A tendency to arthritic attacks with acute and chronic joint manifestations we feel has been somewhat overlooked. One of our patients at present is convalescing from a severe attack of acute inflammatory arthritis complicated with an acute endocarditis and pneumonia. Another suffers with chronic arthritis deformans, and still others have repeatedly complained of mild though definite joint symptoms. Gastro-intestinal disturbances are common; among the more ordinary are attacks of anorexia, headache, apathy, epigastric distress after eating, nausea, and diarrhea. Jaundice sometimes occurs. We have knowledge of an especially interesting case of jaundice which we feel was directly due to zinc intoxication. Unfortunately, we were not able to study it. Among his coworkers the man was known as "yellow-brass Rudy." He was especially subject to the chills, and became markedly jaundiced within a few hours after pouring yellow brass. He could pour red brass without much disturbance, but would not accept, if he could help it, a position where he had to handle yellow brass.

Among the other ill-effects of this vocation we noted a state of malnutrition, a pasty, sallow complexion, and a slight secondary anemia. (The blood cells showed no "stippling.") A well-developed pyorrhea alveolaris was present in all the cases. We detected no changes in the central nervous system, though tabetic symptoms are said to occur. Chronic renal disease should be looked for. Kober found that zinc workers may excrete zinc for months in the urine, though often without signs of poisoning, and Weyl mentions a case showing albumin and a trace of zinc in the urine after a chill. No albumin could be demonstrated during the time the patient was free of the chills. Siegel found a trace of zinc, but makes no mention of albumin in the urine after a chill. Goodman demonstrated the presence of copper, but not of zinc, in the urine and sweat of a brass-worker. The man was probably a finisher and not a molder. As mentioned before, brass-finishers and polishers frequently show visible evidence of copper excretion in the sweat (*i. e.*, greenish tint to skin and hair, staining of underwear, and aggravated itching of the skin). These symptoms are all due in a large measure to uncleanliness, and frequent bathing and the free use of talcum powder tend to prevent their occurrence. The men are not particularly unhealthy.

As the result of examinations kindly made for us by Drs. John Marshall and Wertheim, we are able to report that analyses of the urine from a number of cases revealed no zinc or copper.

It seems that no great tolerance for zinc is ever acquired. Men who have been in the trade for twenty-five years and more frequently suffer from the chills. Certain individuals are more susceptible than others, developing a well-marked chill almost every night and a particularly severe one on Monday nights. None of the subjects experienced the chills when not engaged in their work. About 75 per cent. of the men exposed develop the chills. The general mortality rate among these workers is higher than that among other workmen. One authority says it is two and a half times that of farmers. Sir Thomas Oliver notes that "only ten brass-workers were found living out of 1200 casters in Birmingham who were past sixty years of age, and that a superanuation insurance for brass-founders to begin at fifty-five years of age had only three applicants in a period of some ten years." Hayhurst noted that from among 1761 foundry men the oldest at the trade was seventy-three years of age, that only 17 were past fifty, that 60 were past forty-five, and 180 past forty years of age.

General Conclusions.—Spelter chills lie in the field of preventive medicine. To eliminate them the following precautions should be observed on the part of the employer:

Guard against inhalation and ingestion of metallic vapors by providing the working rooms with an efficient system of ventilation practical for all seasons of the year.

Keep the furnace room apart from the others and provide proper ventilation about the furnaces.

Employ an improved technic for pouring when such is at fault—perhaps some automatic device.

Provide for the removal of all metallic dust and deposits about the foundry by a systematic and thorough cleansing, at regular intervals, of the floor, walls, ceiling, rafters, etc.

Employ strong, healthy men to do the work demanded in brass foundries, zinc smelters, and in any allied trades in which zinc is poured.

Do not employ minors or women.

Do not demand of the workmen an amount of labor that is fatiguing.

Provide proper washing and toilet facilities, and advise the men as to the necessity of their proper use.

Allow the men reasonable time for washing before their eating period and a suitable place for eating.

Caution them to change their clothes before leaving the shop. Advise them not to wear mustaches and to employ respirators when necessary. Caution them against sudden changes in temperature.

A study of industrial diseases is of great importance and should form part of the curriculum of medical schools. With the help of the State, which is now assured in Pennsylvania and in several other commonwealths, it will be possible to inaugurate methods of prevention that will greatly lessen disease and increase the efficiency of the workers.

UNILATERAL RENAL HYPOPLASIA AND DYSPLASIA DUE TO DEFECTIVE ARTERIOGENESIS; RELATION TO SO-CALLED HYPOGENETIC NEPHRITIS.[1]

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The facts embraced in this communication are presented in support of a contention that there is a type of renal anomaly of developmental origin which predisposes to or renders inevitable some form of nephritis, and that this congenital abnormality is probably primarily a defective arteriogenesis necessarily early in the evolution of the organ; furthermore, it is thought that some evidence, based on morphology, is here presented for the first time. The material upon which the report is based represents an accumulation of four years. In order to establish the thesis enunciated it is

[1] Read at the meeting of the Association of American Physicians, May, 1916.

necessary to prove (1) that abnormal kidneys reasonably assignable to such a group occur; (2) that they result from defective arteriogenesis; (3) that they are accompanied by, or lead to, cardiorenal phenomena in at least some degree reasonably attributable to the kidney condition.

Kidneys of the type considered have long been known and variously named, and the congenital origin of many fully accepted. Chopart[2] knew that one kidney might be large, the other small. The earlier observers did not differentiate congenital or primary hypoplasia from sclerotic, inflammatory and other forms of secondary contraction, or atrophy. Indeed the term atrophy, frequently used, is not acceptable; it implies wasting. Some of these kidneys have at no time been larger than when found; such are not wasted organs. As applied to these organs the terms rudimentary, fetal and infantile are also of uncertain interpretation. Teyssèdre[3] used the term renal agenesis; hypogenesis is better. Agenesis should mean absence of the organ, often, however, it is used synonymously with hypogenesis.

LePlay and Fayor[4] call the condition renal disparity and observe that it is an arrest and not an atrophy. Evidently Gastaldi[5] has the same thought and terms it inequality of renal volume, and congenital unilateral atrophy; he restricts these names to kidneys in which both vessels and ureters are present. Braasch[6] evidently recognized this type of lesion, which he included under unilateral atrophic kidney and thought it might be congenital or acquired. Cadore[7] and Gerard[8] include relative atrophy obviously meaning abnormal smallness of one kidney and apply the term absolute atrophy to a more marked lesion. Polack[9] describes the condition of agenesis. Many so-called discoid kidneys[10] belong with this group. Some infantile kidneys of the type described by Geraghty and Plaggemeyer[11] should also be included. The organs and clinical phenomena to which Babes[12] applied the term hypogenetic nephritis and the forms studied by Mironescu[13] and by Jianu and Meller[14] have to do with this type of lesion. The condition is recognized by most authors of text-books; kidneys like those constituting the basis of this article are known to, and adequately described by

[2] Maladies des Voies Urinaries, Paris, 1830; cited by Gastaldi.
[3] Thèse de Paris, 1892.
[4] Bull. et Mém. de la Soc. Anat. de Paris, 1909, T. 84, 339.
[5] Thèse de Paris, 1910.
[6] Ann. Surg., 1912, lvi, 726.
[7] Thèse de Lille, 1903.
[8] Jour. de l'Anat. et de la Physiol., 1903, 39th year, 176.
[9] Thèse de Bordeaux, 1908.
[10] Fèrè, Bull. de la Soc. Anat. de Paris, 1881, 417; Legueu, Bull. de la Soc. Anat. de Paris, 1892, 19.
[11] Jour. Am. Med. Assn., 1913, lxi, 2224.
[12] La Sem. Med., February 8, 1905; cited by Jianu and Meller.
[13] Beit. zum Studium der Histologie der hypogenetischen Nephritis (rumanisch) Bukarest, 1908; cited by Jianu and Meller.
[14] Centralbl. f. allg. Path. u. path. Anat., September 15, 1912, 774.

practically all systematic writers; the basis of defective angiogenesis, however, is not presented as the essential factor in their evolution.

These kidneys are hypoplastic or defectively developed organs; often they are more, the internal arrangement of cortex and medulla is quite anomalous (see Figs. 1, 2, 3, 5, 7), a sort of dysplasia or cacoplasia.

Morbid Anatomy. Although both organs may be involved, hypoplasia is rarely, if ever, bilateral and even where both kidneys are implicated is never truly symmetric; commonly it is restricted to one kidney, the other showing compensatory hypertrophy. Usually the affected organ weighs one-fourth or less, to one-half as much as the other. In five instances I have the weights of both kidneys; the average for the smaller organ is 75.8 gm., and for the larger 140.4; if two cases in which both kidneys are obviously affected be excluded the average weight of the larger kidney becomes 161.3 gms.; the average for the smaller is but little influenced, being 75.4 gms. The most marked difference in weight is 110 gms., the larger weighing in this case 210 gms., the smaller 100 gms. In four cases the smaller kidney weighed 20, 35, 50 and 60 gms. respectively. Teyssèdre[15] observed an instance in which the involved organ weighed 0.85 gm. Gastaldi[16] from computations based on original observation and collated data gives for a man a normal of 152 gms., for left kidney, and 141 gms. for the right.

It is, therefore, obvious that the affected kidney may weigh less than 1 gm. and anything between that and the normal. The whole kidney need not be involved (several kidneys show this, notably the upper in Fig. 5); one pole may be practically normal or at most but little affected. Anomalies of the genitalia[17] usually unilateral and on the side of the hypoplastic kidney, frequently accompany renal anomalies of this type; in case recorded by Lombroso[18] the renal defect was on one side and the genital abnormality on the other. Renal dystopia and misplacements of ovaries or testes have also been noted.

The accompanying reproductions (Figs. 1 to 6 inclusive), from photographs, are, in each instance, one-half normal size and adequately illustrate the gross morbid anatomy. An epitome of known data is included in each legend. I have photographs of all specimens studied; this publication includes a few typical specimens only. With the exception of one pair all the organs are in the Museum of the Jefferson Medical College. As much histologic description as may be necessary to present the vascular changes and their results will be given when discussing defective arteriogenesis.

Of Gastaldi's 66 cases, 10 were females, 32 males and in 18 the sex was not stated. In my series 5 were males, 4 females. Including

[15] Loc. cit. [16] Loc. cit.

[17] Secher, Berl. klin. Wchnschr., 1915, 52d year, 487; Jainu and Meller, Centralbl. f. allg. Path. u. path. Anat., September 15, 1912, 774; Besançon, Thèse de Paris, 1889.

[18] Cited by Winter, Arch. f. klin. Chir., 1903, Bd. lxix, 6111.

the 9 cases on which this report is based, 60 cases have been identified in which the kidney involved is known: 32 right, 28 left. Of 9 patients here reported 3 were negroes.

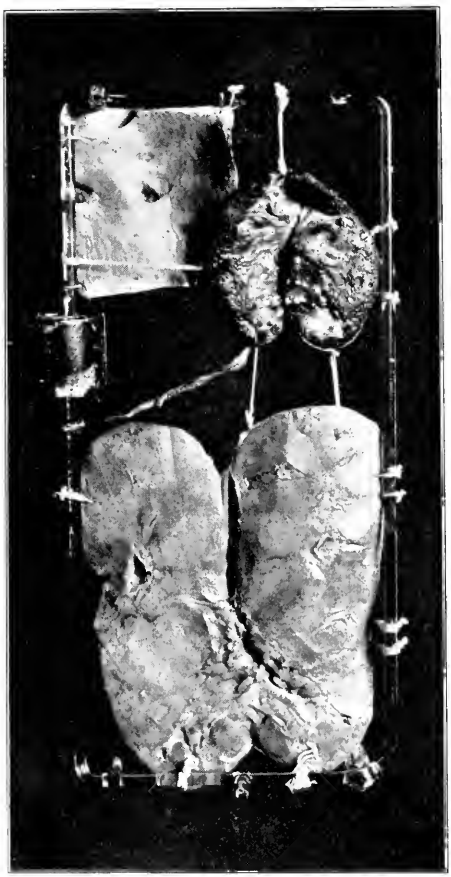

FIG. 1.—Incised surface of kidneys, neither normal; upper organ of infantile type. One-half natural size. M. J.; female; white; aged seventy-three years. Patient and husband insane. Arteriosclerosis; tuberculosis; tuberculous peritonitis. Cardiorenal symptoms (dropsy, stupor, uremia); death. Urine pale: specific gravity, 1010; albumin and casts. Postmortem: Arteriosclerosis. Heart 510 gms. Right kidney (upper) 20 gms. Left kidney (lower) 120 gms. Duplicated renal vessels on both sides. Right kidney of infantile type; vessels nearly obliterated. Distinctions between cortex and medulla imperfect and arrangement abnormal in both organs. Open aorta with abnormal orifices of renal arteries above and to left. See also photograph of other aspect shown in Fig. 2. (Museum No. 1637.)

Concerning the second proposition, namely, that the abnormal kidneys result from defective arteriogenesis, the evidence must be more carefully weighed. The time is past when doubt as to the vascular origin of certain forms of nephritis can be entertained; arteriosclerotic kidney is universally accepted. When, in this condition, one kidney is much more changed than the other, or one

renal artery more sclerotic than its mate, or, as is not unknown, when a branch of one renal artery, distributed to one pole of one kidney, is more sclerotic than other branches to other parts of the same kidney, is it not reasonable to assume that some congenital or essential developmental peculiarity has determined the asymmetric

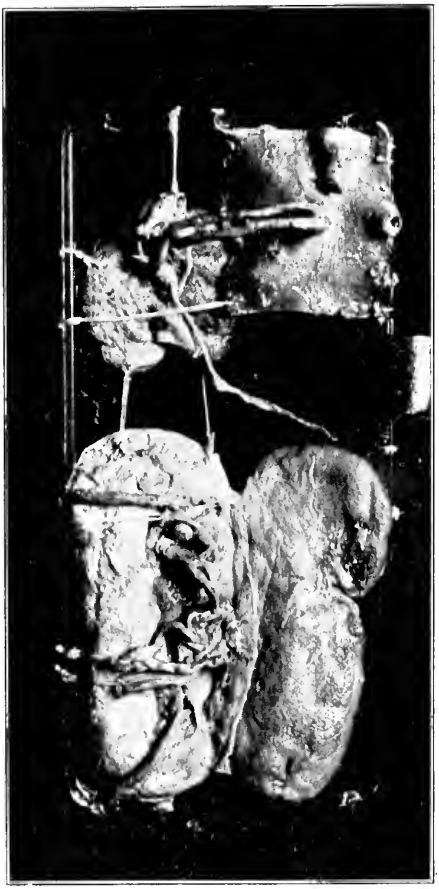

FIG. 2.—One-half natural size. External aspect of opened kidneys shown in Fig. 1. Above and to right external aspect of opened aorta. Smaller kidney supplied by two renal arteries both small and cord-like. Artery to larger kidney came off from aorta as a single trunk dividing at once into two branches both of which are shown on left half of lower organ. Trunks and branches show notable sclerosis superimposed on a congenital anomaly. Clinical data are given in text and in legend to Fig. 1. (Museum No. 1637.)

distribution of the lesion? The pressure in both arteries must be balanced, the toxicity of the blood, the irritant, destructive or other noxious agents in that fluid must be proffered alike to both arteries and to all branches of the same artery, so that if differences are found the reasonable assumption is that they resulted from peculiarities of the affected vessel. Resting on known facts deduction necessarily

leads to the conclusion that developmental peculiarity must be a determining factor.

For about a quarter of a century through succeeding editions, Osler[19] has maintained that some patients have better vessels than others; it is reasonable to believe that in the same patient some

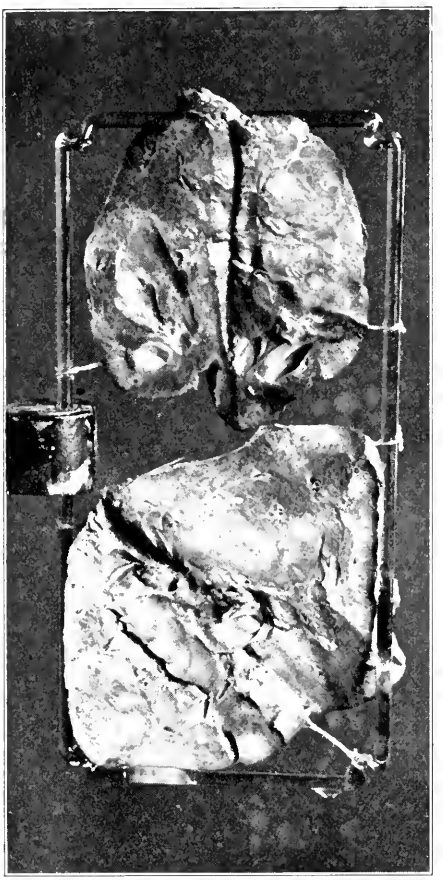

FIG. 3.—Both organs hypoplastic and dysplastic; superimposed alterations of secondarily contracted (arteriosclerotic) kidneys. One-half natural size. Female; colored; aged thirty years. Brought to Hospital in convulsions; unconscious; unequal pupils; urine contained albumin. Coroner's case. Death attributed to septic embolism from infected finger. Postmortem: Pneumonia; pleurisy. Heart weighed 350 gms. No evidence of embolism and no thrombosis found. Moderate arteriosclerosis. Right kidney (upper) 50 gms. Left kidney (lower) 130 gms. Distinction between cortex and medulla possible at points only. (Museum No. 615.)

arteries may be better than others. Lancereaux[20] clearly recognized a relation between congenital narrowing of the vascular tree

[19] Principles and Practice of Medicine, 1892, 664; Osler and McCrae, Principles and Practice of Medicine, 1916, 8th ed., 842.

[20] Art. Rein. du Dict. Encyclop. des Sci. Med., 1876, 3me Serie, T. 3, 216.

and nephritis, observing that in some patients the former is at first accompanied by chlorosis, and later by albuminuria with atrophic sclerous nephritis. Gancher,[21] Rayer[22] and Besançon,[23] contended

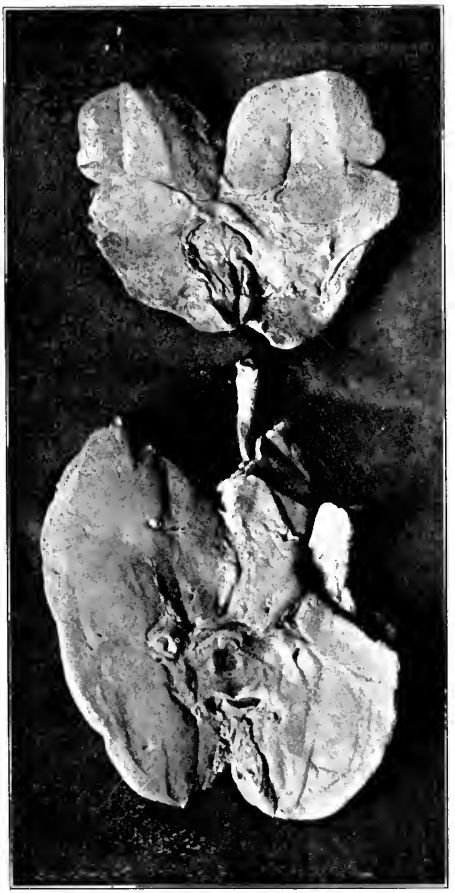

Fig. 4.—Presented through courtesy of Prof. Stengel, Prof. A. J. Smith and Dr. Weidman. One-half natural size. E. H.; female; white; aged twenty-one years. "Always had kidney trouble." In 1912 when six months pregnant, toxemia, albuminuria, miscarriage. January, 1914, therapeutic abortion for toxemia, albuminuria, etc. Blood-pressure known at that time to exceed 212. Recovery with high blood-pressure. Readmitted in August and again in December, 1914. Quantity of urine varied from 750 c.c. to 2825 c.c. Specific gravity, 1007–1010; blood in urine once. Phthalein 33 per cent. in two hours. Wassermann negative. Clinical Diagnosis: Arteriosclerosis; chronic interstitial nephritis. Postmortem: Death due to thrombosis of intestinal vessels. Heart 470 gms. Left kidney (upper) 35 gms. Right kidney (lower) 80 gms. See also text. Sclerotic changes superimposed on congenital anomaly. (Museum No. 2632.)

for a nephritis due to arterial aplasia. Rayer noted a relation between size of the renal artery and the kidney supplied, and that in

[21] Cited by Besançon. [22] Ibid. [23] Thèse de Paris, 1889.

the same individual the two arteries as well as the organs supplied differed correspondingly in size; of course, this is known to every morbid anatomist. I am not so sure that Gaucher's allusion to nephritis resulting from primitive alteration of anatomic elements

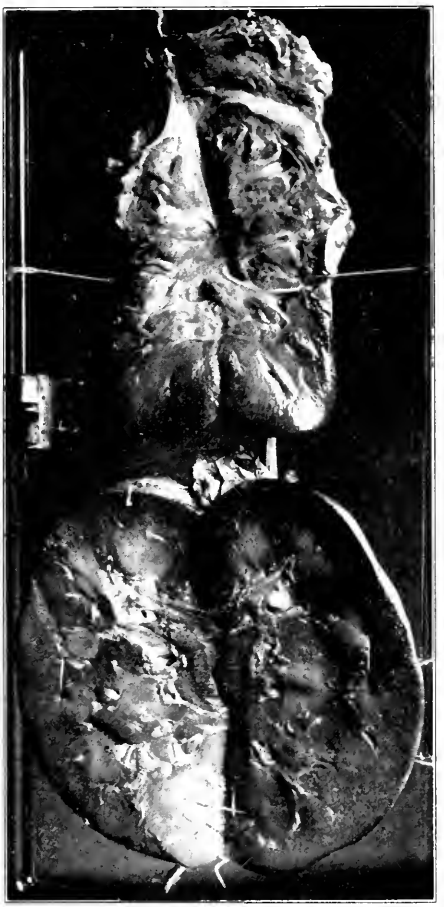

FIG. 5.—One-half natural size. M. S.; male; colored; aged forty-eight years. Cardiorenal case; gastric symptoms predominated early; later dropsy; dyspnea; systolic murmur. Polyuria; trace of albumin; casts; anemia. Diagnosis: Pernicious anemia; syphilis of liver. Postmortem: Hydropericardium; hydrothorax; ascites; gumma of liver. Heart 418 gms. Arteriosclerosis. Left kidney (upper) fused with adrenal, combined weight 132 gms.; 2 arteries, 2 ureters separate to bladder; upper half hypoplastic and dysplastic; small segment of lower pole is practically normal. Right kidney (lower) 198 gms. Slight dysplasia but organ distinctly hypertrophied. (Museum No. 905.)

refers to defective bloodvessels as the essential basis. Besançon is perfectly clear; to him a subnormal arterial function exerts a deteriorating influence on the kidney, increases its susceptibility to toxic bodies, and may alone determine a primitive interstitial

nephritis. He formulated an accompanying clinical picture. Babes[24] notes that walls of renal arteries may be thicker or thinner than normal and that the musculature is usually hypertrophic. The arterial dysplasia so obvious in some of my specimens is quite

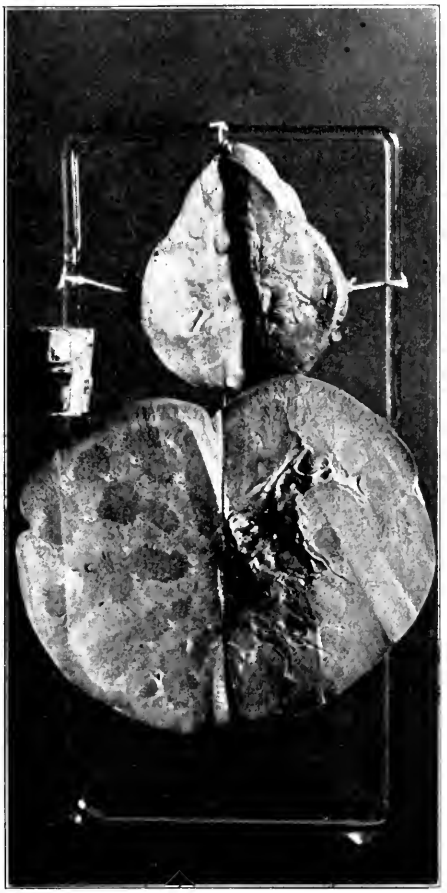

FIG. 6.—One-half natural size. E. D.; female; colored; aged eighty-two years. Had five children; all dead. Disabled by rheumatism. Pain in body and limbs. Edema of legs; ascites; albuminuria; casts; lobar pneumonia; death. Postmortem: Heart 320 gms. Advanced arteriosclerosis. Pneumonia. Left kidney (upper) 110 gms.; hypoplasia and dysplasia; surface but slightly granular. Right kidney (lower) 200 gms. Note absence of normal renal marking; disorderly arrangement of cortex and medulla. Notwithstanding the rather advanced arteriosclerosis neither of these organs is typic of that condition. The larger is clearly hypertrophied, without conspicuous interstitial fibrosis; sections show a degenerative lesion affecting the tubule epithelium with negligible interstitial change; slight glomerular fibrosis. (Museum No. 466.)

characteristic. As stated above my contention is that this is the essential feature; probably all else is secondary. Osteogenesis

[24] Loc. cit.

imperfecta and neurogenesis imperfecta are both fully recognized; why not, as a basis of many anomalies, a defective arteriogenesis? In some instances veins and possibly capillaries are also implicated—defective angiogenesis.

The organ from which was taken the section depicted in Fig. 7 was removed because of recurring attacks of pain; the case, under the care of Prof. Stewart, will be fully reported elsewhere. The anterior aspect of the kidney showed typic appearance of defective nephrogenesis; the artery figured is from within affected side of organ. Observe fragments of elastica in perivascular tissue, irregular

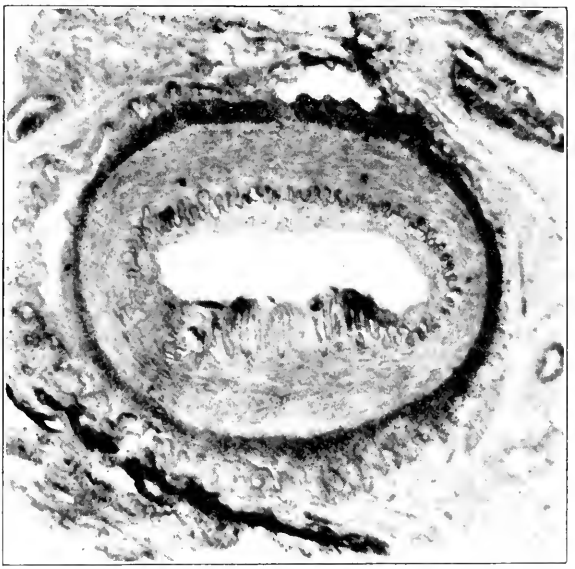

Fig. 7.—Artery supplying involved area of a kidney removed at operation. Fragments of elastica in paravascular tissues; diffuse lime deposit (black) to left and below artery. External elastica almost straight band. Muscle stratum mostly fibrous. Internal elastica atypic, with long sweeping irregular waves notably below. Subintimal proliferation especially marked above. Patient suffered from what was thought to be renal pain or renal angina. Photomicrograph. (Museum No. 2183–B; anterior vessel.)

external elastic lamina of uneven thickness and notably deficient in waviness. The muscle is abnormally thick and contains more fibrous tissue than muscle. The internal elastic lamina is nowhere perfect and below shows long irregular sweeps never seen in normal vessels. Fig. 8 is a smaller vessel from the same organ; the muscle layer is thick, the elastic lamina (but one layer is present) is irregular and imperfect; a considerable arc (lower left) is without elastica; between elastica and endothelium is a fibrohyalin stratum resembling the substance observed by Gull and Sutton. Of course the arteries shown are not normal; were they ever so? I doubt it.

Fig. 9 (section from organ shown in Fig. 1) shows three arteries,

none possessing a lumen proportionate to its size, nor having a normal or vestige of normally distributed elastica; in none is the muscle or intima normal. The organ contained some lime and consequently the section is torn. Below and to the left are groups of hyalin tufts, and a few tubules, two of which are dilated; other tubules containing hyalin are shown near the center. Of course, this patient was old (seventy-three years) and her arteries advancedly sclerotic. The opposite renal artery appeared as sclerotic as those of the small symmetric, miniature or infantile kidney which was

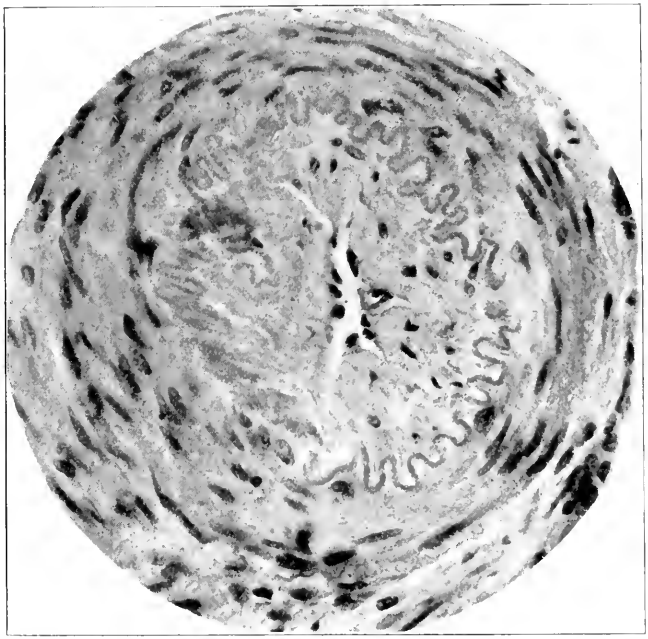

Fig. 8.—Small artery from same case as Fig. 7. Note thick muscle layer; single elastic lamina, imperfect, atypic, and absent from segment below and to the left; break to right; abnormal waviness. Between elastic lamina and slit-like lumen marginated by endothelium note thick fibrohyalin stratum which microchemically gives usual collagen reactions. Arteries from posterior part of this organ did not show these characters or at most but slightly. Photomicrograph. (Museum No. 2183-A; anterior vessel.)

probably hypoplastic at birth or became so shortly afterward; the lesions of arteriosclerosis are superposed. Fig. 10 is of artery from upper pole of organ shown in Fig. 5. The distorted cortex, thickened capsule, irregular surface, unevenly distributed medulla, and abnormal pelvis of upper half of organ shown in Fig. 5, might have been attributed to the associated arteriosclerosis; however, the fused adrenal extending into the kidney substance could have had no such origin. The artery shown in Fig. 10 possesses a single irregular imperfect elastic lamina inside of which is a thick muscle layer; fragmentation of intima seen in many of these vessels is

probably due to contained lime salts. I do not believe that this was ever a normal vessel. In Fig. 11 are two vessels in the midst of a mass of fibrohyalin tissue; the stainable elastica is without its characteristic waves, notwithstanding the fact that obviously both vessels are contracted. To the left is part of another vessel, an artery, with the waveless internal elastica upon which is a thin cellular layer covered by endothelium. Fragments of the external elastic lamina extend into the surrounding fibrous cellular tissue. In the center of the picture is a cellular area; below and to the left several imperfectly developed Malpighian tufts Photograph of section from small kidney is shown in Fig. 6.

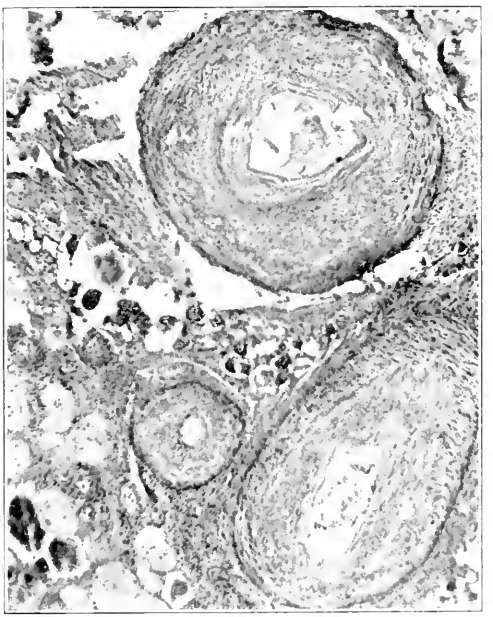

Fig. 9.—Section from kidney shown in Figs. 1 and 2. Three abnormal vessels, apparently arteries. See description in text. Note that normal arrangement of lamina is not present nor are the normal layers recognizable. Below larger vessel note calcified content of degenerated tubules; practical absence of normal epithelium. Below to left many hyalin tufts. Photomicrographs. (Museum No. 1637–8–1.)

The contention is that these kidneys were never perfectly developed, that the arteries were always defective, and that probably the renal hypoplasia rested upon a nutritive basis. Patients may reach an extreme old age without manifesting symptoms, but when anything calls upon the organs for unusual functional activity they break down. Such functional inadequacy is well known in congenital heart disease, in the liver when altered by congenital syphilis, and in allied conditions. Meltzer[25] has shown that in many organs,

[25] Jour. Am. Med. Assn., 1907, xlviii, 655.

notably the kidneys,[26] there is a generously beneficent excess of our actual needs. We may by various morbid processes diminish the abundance perilously close to the danger-point. It is equally certain that the patient may be born without the generous supply usually afforded, or, if adequate at birth, faulty or arrested development of the kidney may later exert a crippling influence. It is in such position that these patients find themselves. They may pass through life with no renal manifestation, and in such cases the

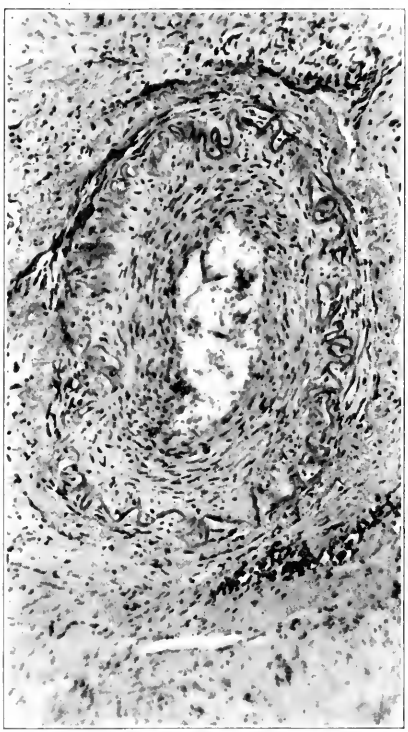

Fig. 10.—Transverse section of artery from upper pole of smaller kidney shown in Fig. 5. Fragments of elastica in paravascular structures; vessel elastica atypic in location and morphology. No muscle external to elastica and abnormally thick fibromuscular stratum between elastica and lumen. Completely detached endothelium. Tissue around vessel is formative in type, contains fibroblasts in varying stages of development. Photomicrograph. (Museum No. 905–3.)

symptomatology which Besançon[27] and also Jianu and Meller[28] and others have attempted to establish, may be absent. Of 9 cases embraced in this study in 3 renal disease was clearly indicated, and in 1 the diagnosis of chronic interstitial nephritis was made with full recognition of associated cardiovascular phenomena; in another the

[26] This phase of renal function is fully discussed by Karsner, Bunker and Grabfield, Jour. Exp. Med., 1915, xxii, 544, who also give references to earlier work.

[27] Loc. cit.

[28] Loc. cit.

diagnosis was chronic nephritis. One of the patients was brought to the accident ward, admitted unconscious with a provisional diagnosis of uremia, and died during transfer to the ward. In this case no doubt a careful study would have resulted in recognition of the condition. One of the patients operated upon (not one of the 3 just mentioned) had been explored and, because the posterior part of the kidney was normal and the anterior alone affected, the condition was not recognized even at operation. The most carefully studied case in the group is the one for which I am indebted to Prof. Stengel.[29] Pregnancy, associated toxemia and eclampsia, with the report that she had had kidney trouble all her life, were

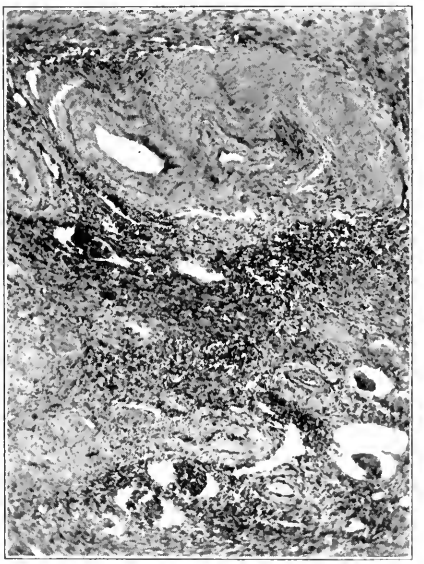

FIG. 11.—Insular fibrosis surrounding small group of imperfectly formed vessels. In center mononuclear infiltration. Below many fibrohyalin glomeruli; others are cellular in centers of dilated tuft spaces. Photomicrograph. (Museum No. 466.)

suggestive; a systolic pressure above 200 mm., and at one observation 230; a trace of albumin; low specific gravity; phthalein elimination 40 per cent. in two hours; non-protein nitrogen 33 to 36 mgs. per 100 c.c. It is probable that ureteral catheterization might have cleared up the case. Besançon[30] lays particular stress upon history of chlorosis or of a chlorotic appearance, headache, vomiting, lassitude, slightly puffy eyelids, slight diffuse edema of lower extremities, frequent micturition, pale abundant urine; obviously none of these alone, nor all together would constitute anything peculiar or characteristic. Nephritis, toxemia, or uremia,

[29] Prof. Stengel was kind enough to permit me to examine the clinical history and make the necessary abstract. I am indebted to Prof. Allen J. Smith and Dr. Fred D. Weidman for the privilege of studying the specimen.

[30] Loc. cit.

coming on in young persons without adequate cause should arouse suspicion. Obviously the Roentgen ray and a careful differential study of excretion from the two ureters would be of distinct aid in diagnosis. By the use of these modern methods Dr. Alexander Randall has recognized the condition and has operated upon a patient having renal abnormality apparently of this type. With well-known functional tests at present at the disposal of the clinician it would seem that the condition should be recognized, and that, with a knowledge of the possibility of such an anomaly, a closer scrutiny of atypic cardiorenal cases should result. Because of operative risk incident to attack upon the better kidney the condition must be of particular interest to the surgeon.

THE RARITY OF CONJUGAL PHTHISIS.

By Maurice Fishberg, M.D.,

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During fifteen years of service as physician to the United Hebrew Charities of New York City I have had under observation over 800 tuberculous patients annually, most of them married, and a considerable proportion having quite large families. At the beginning of the service, influenced by the current teachings of the dangers of exposure, every consort of a tuberculous patient was suspected of having contracted the disease. The least indication of trouble pointing to the respiratory tract was sufficient to suggest phthisis, and a diagnosis of this disease was made more often than was justified by the subsequent observation of the cases. But with increasing experience among this class of patients I became convinced that tuberculosis in both husband and wife is exceedingly rare, and I drifted to the other extreme—the fact that a woman has a husband with active phthisis would not influence me in interpreting doubtful symptoms and signs in favor of making a diagnosis of this disease because of the exposure to infection to which she has been subjected.

An investigation three years ago[1] showed that the children of these dependent consumptives are infected with tuberculosis to the extent of 84 per cent. when they reach the age of fourteen. The consorts of these tuberculous patients have been found almost invariably "reactors." Bearing in mind that while a positive reaction to tuberculin is conclusive evidence that the person has been infected with tubercle bacilli at some previous period of his or her life, but it by no means shows that the patient is sick as a result

[1] Fishberg, A Study of the Child in the Tuberculous Milieu, Arch. Pediat., 1914, xxxi, 96, 197; 1915, xxxii, 20.

of this infection, it appeared to me rather paradoxical: The children are nearly all infected; the consorts all show conclusive evidences of harboring tubercle bacilli in their bodies, yet phthisis in both husband and wife is so rare as to warrant investigation. Moreover, the children, especially infants living with parents who suffer from active phthisis, are nearly all suffering from some form of tuberculosis, and an enormous proportion succumb, particularly to the meningeal form. Still, the husband of a tuberculous wife, or the wife of a tuberculous husband is only exceptionally affected with the same disease.

This is a fact which is not well known and, in general practice, as well as in the various tuberculosis clinics in this country, the consorts of tuberculous patients are always suspected of being phthisical. It appears that a statistical investigation of this problem may prove of value, and may perhaps stimulate others to collect similar statistics, considering that opportunities for such investigations are abundant in the numerous tuberculosis clinics and sanatoriums in any city of this country.

The tuberculous patients reported on in this paper were mainly dependent people, supported wholly or partly by the United Hebrew Charities. Their dependency was in most cases the result of tuberculosis. At first it was projected that about 500 should be examined, but when it was found that our general impression was fully confirmed when 170 couples were examined, I deemed it safe to report on this number, feeling confident that an increase in the number would not materially alter the result.

Inasmuch as the problem of exposure is most important when speaking of the transmission of tuberculosis, it must be mentioned that these patients were of the same class; in fact, a large number were the very families, which were investigated three years ago as to the incidence of tuberculosis in their offspring. At that time we found that they averaged 3.3 rooms per household, or 1.57 persons per room, the size of which was, in the vast majority of cases, the minimum that can be found in New York City tenements, and many of the sleeping rooms had no windows communicating directly with the external atmosphere. Another way of showing the mode of life of these tuberculous and dependent families is by mentioning that counting all the beds, cribs, couches, etc., it was found that there was only 0.58 of these articles of furniture per person.

We thus find that there were present practically all the factors which favor the dissemination of tuberculosis, and most of the factors predisposing to the development of phthisis, namely, overcrowding in dingy tenements, poverty with its concomitant malnutrition, etc.

Of the 170 consumptives, 9 were women and 161 men. In the latter group we found that 78 of the wives lived with their tuberculous husbands at home, and of these 51 slept in the same room with their sick husbands, and 23 even shared their beds with them.

Of the rest, 27 of the tuberculous husbands were inmates in sanatoriums and hospitals for consumptives and 5 were away from home, though not in institutions. An inquiry was made whether cohabitation has taken place since the onset of the disease in the sick partner, and it was ascertained that 146 acknowledged that such was the case while the rest denied it, though we have good reasons to believe that most of them were not truthful in this respect. We also found that during the time of the illness of the affected consorts, 48 children were born to these couples and two women were pregnant at the time this investigation was made—51 of the women were widows, having lost their husbands through phthisis.

Among the 9 men who had phthisical wives 1 wife was found suffering from active tuberculosis in the advanced stage. But a careful inquiry revealed the fact that she was phthisical before the disease developed in the husband. We have a record of several examinations of this woman for six years back, and she showed symptoms of phthisis until one year ago, while her husband was fairly healthy. At this examination a large dry cavity was found in one of the upper lobes of her lungs, so that if any transmission had taken place it was from the wife to the husband. The other 8 husbands showed no symptoms or signs of tuberculous disease.

Of the 161 wives of tuberculous husbands four were phthisical, though in only one the lesion in the lungs showed signs of activity, while in the other three it was either quiescent or arrested.

It is thus seen that only 2.5 per cent. of the wives of 161 phthiscial husbands were found to be suffering from the same disease, despite the fact that they have been exposed to infection more than women with healthy husbands.

A review of the literature on the subject shows that previous investigations of this character were in most cases in agreement with our results. Soon after Koch's announcement of the discovery of the tubercle bacillus, many of the best clinicians of those days stated that their experience had led them to the conviction that tuberculosis is not a transmissible disease, because it is exceedingly rare to find that a married tuberculous patient should transmit it to the healthy consort. But soon there appeared in medical journals many cases showing that such transmission is not uncommon. Instead of giving detailed histories of such cases we will quote Wilson Fox's[2] summary of the evidence on this point:

"A. One phthisical man married several times, most of his wives becoming phthisical—13 cases.

"B. Consumptive man who died transmitted to wife; widow infected second husband—3 cases.

"C. Man infected wife and died. Widow remarried and also died of phthisis, as did her second husband after he had remarried. His widow lived and also married again, and the next husband died of phthisis.

[2] Diseases of the Lungs, London, 1891, p. 571.

"D. Woman married in succession two phthisical husbands, and became phthisical after the death of the last—2 cases.

"E. Wife consumptive, died, having infected husband, who also infected a second wife—10 cases.

"F. Consumptive wife before dying infected her husband, who later infected a second wife. This widow afterward infected a second husband—1 case.

"G. Woman died of consumption. The widower, not stated to be phthisical, married subsequently three other wives; total four wives, of whom the first, second, and third died of phthisis, but the fourth wife, and apparently the husband, remained free from the disease."

Such cases have been reported by the hundreds in the medical journals of twenty-five years ago. But it must be acknowledged that they are not conclusive proof that phthisis is more frequent among the consorts of the tuberculous than among those who are married to non-tuberculous persons. Single isolated cases of the coexistence of the same disease in both husband and wife may be found in any other pathological processes. We have only to mention *cancer à deux* or conjugal cancer, cases of which have been reported in abundance. But it is the consensus of opinion that in these cases the cancer was not transmitted from one partner to the other. In J. Wolff's[3] great work on cancer, as well as in W. Roger Williams's[4] book on the same subject, we find numerous cases of conjugal cancer which read like the above-mentioned cases of marital phthisis. Similarly, Betz, Oppler, Boisumeau, R. Schmitz, C. Külz, cite details of cases of conjugal diabetes, but an analysis by H. Senator[5] shows conclusively that they do not prove the transmissibility of this disease and that they are merely coincidences.

The only satisfactory way to study the problem of marital phthisis is the statistical. If we find that a large number of consorts of consumptives develop the same disease, we may conclude that it has been transmitted from the sick to the healthy consort.

A careful search of medical literature has revealed the following data about conjugal phthisis:

Austin Flint, Sr.,[6] found only 5 among 700 cases of phthisis in which there was room for the suspicion of the disease having been communicated from the husband to the wife or the wife to the husband. Reginald Thompson[7] found among 25,000, 15 cases of phthisis in both husband and wife, "so that the proportion of infective cases may be reckoned as not less (probably a little more) than one per mille." In his extensive experience Wilson Fox[8] had

[3] Die Lehre von der Krebskrankheit, Berlin, 1914, ii, 58.
[4] The Natural History of Cancer, London, 1908, pp. 194, 262.
[5] Berlin. klin. Wchnschr., 1908, xlv, 133.
[6] On Phthisis, Philadelphia, 1875, p. 419.
[7] Lancet, 1880, ii, 727.
[8] Loc. cit., p. 561.

only met two instances of conjugal phthisis. In one he had only heard that a wife had died of phthisis whose husband, still living, was seen by him five or six years before with a cavity after an acute attack, but he did not know her family history. In the other case the wife died of acute tuberculosis about one year after her husband's death, but she was a member of a family which he knew to be phthisical. When mentioning this fact, he adds significantly, "my experience now extends over twenty-seven years." Leudet's[9] experience was to the same effect: Investigating the subsequent history of 112 widows and widowers whose partner died from tuberculosis he found all alive and not developing any symptoms or signs of phthisis. He concludes that among the well to do classes, who live in comfort, in healthy homes and are well-nourished infection with phthisis is extremely rare.

Sir Hermann Weber[10] collected statistics on this subject. He found in the history of "68 persons, male and female, who with more or less pronounced consumptive taint have married healthy partners. One of the several of the partners of 10 of these 68 cases became consumptive. The question, however," he says, "takes a different aspect if the originally tainted husbands and wives are considered separately. Of the 68 persons, 39 were husbands, 29 wives. Only one of the husbands became diseased, while of the wives 9 out of the 39 husbands became affected. These 9 husbands lost 18 wives, namely, 1 lost 4 wives, 1 lost 3, 4 others lost 2 each, and 3 only 8 each."[11]

An analysis of these figures is not productive of conclusive results on the problem of the transmission of phthisis from husband to wife. It seems that many of these husbands were sufficiently resistant to the disease as to live long enough to fatally infect more than one wife; the wives were, on the other hand, very vulnerable, which would point rather to either a series of coincidences, considering the small number of cases reported, or that they were a select group, studied for the purpose and selected because of the striking features they presented.

Conclusive proof would only be a large number of cases taken at random. Such a series of cases were reported by I. Burney Yeo.[12] He collected particulars of 1055 cases of consumption which had come under his observation consecutively in the hospital. Of this

[9] Gaz. hebd. de méd., Paris, 1890, xxvii, 102.

[10] On the Communication of Consumption from Husband to Wife, Tr. Clin. Soc., London, 1874, vii, 144.

[11] It appears that cases in which a tuberculous husband lost several wives in succession through phthisis are very abundant in medical literature. They appear to confirm Pearson's theory of sexual selection, or "assortative mating" as he calls it, and indicating that persons with phthisical constitutions are attracted by others with the same taint. This point will be discussed later on in this paper. Wilson Fox (loc. cit., p. 572) says: "The group of husbands to many wives would appear to me to point even more strongly to one common cause other than contagion."

[12] Contagiousness of Consumption, Brit. Med. Jour., 1882, i, 895.

number 621 were males and 433 were females. Of the males 306 were married, 297 were single, and 18 were widowers; about 3 per cent. of the whole, and about 6 per cent. of those who had been married. Of the 18 widowers 2 only could state positively that they had lost their wives by consumption and one of these wives had been dead thirteen years; 6 of them had lost near relatives by consumption (father, mother, brother, or sister) giving a presumption in favor of hereditary predisposition, and in 10 no precise information could be obtained. Of the 434 females, 199 were married, 206 were single, and 29 were widows; the widows being about 7 per cent. of the whole, and about 15 per cent. of those who had been married. Of the 29 widows, 5 only were able to state positively that their husbands had died of consumption, 1 lost her husband in a 'fit,' 6 had lost near relatives by phthisis, and 17 could give no precise information.

Yeo also quotes statistics of J. P. Barlett who found that among 94 males in the hospital with phthisis, 53 were married, 37 were single, and 4 were widowers; of these 4, 2 had lost their wives by consumption. Of the 53 whose wives were alive, all the wives, except 2 were quite healthy. Of the 83 females who were then in the hospital with consumption, 62 were single, 15 married, and 6 widows; of the 6 widows 3 had lost their husbands by consumption; in 2 of the 3 there was marked hereditary predisposition; and in 1 there was none; in the remaining cases the husbands were healthy.

"Taking these figures for what they are worth," concludes Yeo, "it seems certain that the communication of consumption from wife to husband, even among the class in which the conditions of life favor to the utmost the communication of contagious disease, is very rare; while it would seem that communication (assuming for the sake of argument, the disease was really communicated) from husband to wife is more frequent."

More recent investigations appear to bear out Yeo's conclusion. Thus of 159 couples in which one of the partners was tuberculous, Brehmer[13] found that in 19 or 12 per cent. both suffered from the same disease. Haupt[14] found in 417 cases 22, or 5.2 per cent., in which both partners were affected with phthisis, which is not above the normal number expected in the average population irrespective of excessive exposure. Only Cornet[15] found among 594 couples that in 23 per cent. of cases both partners were tuberculous which is double that found by Brehmer and he explains the disparity by the fact that his patients were hospital cases, *i. e.*, of the poorer starta of population while those of Brehmer and Haupt were well-to-do private patients.

[13] Therapie der Chron. Lungenschwindsucht, Berlin, 1885
[14] Deutsch. med. Ztschr., 1890, p. 340.
[15] Tuberculosis, American edition, 1904, p. 265.

There are other statistics available on this subject. Ch. Mongour[16] found among 440 married couples in which one of the consorts was sick with phthisis, there were 16 in which the partner was also affected, *i. e.*, 4 per cent. W. Thom[17] found among 402 married couples only 12, or 3 per cent., in which the partners had in all probabilities contracted the disease from their consorts. Meissen found probable infection in 5 per cent. of married tuberculous patients. Jacob and Pannwitz,[18] in a collective investigation in several German sanatoriums admitting patients from all classes of society, that in 8.5 per cent. conjugal phthisis could be found.

An excellent statistical work on this subject was published by Wilhelm Weinberg,[19] who found that among 1426 husbands of tuberculous wives 118, or 8.3 per cent. died from this disease; among 2506 wives of tuberculous husbands 112, or 4.5 per cent., succumbed to this disease. Among a total of 3932 consorts of tuberculous persons, 230, or 5.9 per cent., died from tuberculosis. He thus finds that the mortality from phthisis among those who are married to consumptives, is about double that observed in the general population. Taking the elements of age, sex, etc., into consideration he found that among these 3932 individuals only 2.7 per cent. are expected to succumb to tuberculosis and not 5.9 per cent., as was actually the case. He concludes, therefore, that marriage with tuberculous individuals though not as risky as is generally supposed, yet it is not always harmless. Though he emphasizes that his material shows that not all the tuberculosis thus acquired is due to direct infection from the consort; hardly one-third can be attributed to this cause.

Frier[20] adopted a statistical method similar to that of Weinberg, and found that cancer shows the same double ratio of mortality when its incidence among married couples is calculated according to the theory of probability. After the death of the patients the number of the consorts who succumb to cancer is three times as large during the first year; twice as large during the first five years, etc. Thus the theory of probabilities, as worked out mathematically, yields the same results in cancer as in tuberculosis, which is apparently a confirmation of Pearson's theory of assortative mating spoken of elsewhere in this paper.

Riffel investigated for 200 years backward the demography of a German village with 1200 population. C. Kirchner calculated from his figures that there were 110 tuberculous families among a total of 716, *i. e.*, 15.36 per cent. From these figures it would appear

[16] Recherches statistiques sur la contagiosité de la tuberculose pulmonaire, Congr. internat. de la tuberculose, Paris, 1905, i, 413.

[17] Beitr. zur Frage d. Tuberkulose-ansteckung unter Eheleuten, Ztschrft. f. Tuberk., 1905, vii, 12.

[18] Enstehung und Bekämpfung der Lungentuberkulose, Berlin, 1904.

[19] Lungenschwindsuch beider Ehegatten, Beitr. z. Klin. d. Tuberk., 1906, v, 365.

[20] Quoted from F. Martius, Handbuch der Tuberkulose, Leipzig, 1914, i, 404.

that the wife is more likely to contract the disease from her husband than the reverse which is in agreement with Yeo's and Weber's observations mentioned above. On the other hand Jacob and Pannwitz found that in 142 cases in which the husband was tuberculous before marriage, 133 of the wives remained in good health, and in 24 cases in which the wife was tuberculous before marriage the husband became phthisical in 9 cases. Our figures show that the wife is not excessively liable to contract phthisis because of living with a phthisical husband.

Excellent studies of the risk of infection with tubercle within the family were made by Charles Goring[21] and Pope, Pearson, and Elderton.[22] They calculated the data in the records of the Eugenic Laboratory in England and studied the "degree of resemblance," in this case referring to the presence or absence of tuberculosis in both members of the compared pair, between husband and wife. Inasmuch as their methods of treating statistical figures are above reproach, their results are very interesting and instructive. The net results of their studies were that "there is a much lower 'resemblance' between husband and wife in the matter of tuberculosis than between parent and child, say from 0.25 to 0.30, and yet the intimacy of husband and wife is in most cases a closer one." "The first relation," concludes Karl Pearson, "is precisely that which we find for other characters where the relationship is due to heredity; the second relation is precisely that which we find for other marital resemblances, say insanity. It is therefore difficult to believe it to be due to infection." From extensive and carefully collated statistics Pearson[23] found that as we go downward in the social scale the chances that a tuberculous husband will have a tuberculous wife diminish. This is, however, observed in most other traits of the partners, and has been attributed to sexual selection, or "assortative mating," as Pearson terms it. He found that husband and wife resemble each other in the psychical as well as the physical characters. Common environment can hardly give husband and wife the same eye color, nor the same stature, nor length of cubit—these were determined before marriage. Inasmuch as this selection is largely an intellectual one and has no existence among the poor, it is most prominently observed among the well-to-do and intellectual classes. In other words, Pearson found that phthisical stock is attracted to and mates with phthisical stock. Paul Römer,[24] discussing this problem from another angle, arrives at practically the same conclusion.

The rarity of marital phthisis has been one of the most important stumbling blocks in the teachings of the transmissibility of tuberculosis. We have already mentioned that it was at one time brought

[21] On the Inheritance of the Diatheses of Phthisis and Insanity, London, 1909.
[22] A Second Study of Pulmonary Tuberculosis; Marital Infection, London, 1909.
[23] Tuberculosis, Heredity and Environment, London, 1912.
[24] Beitr. z. Klin. d. Tuberk., 1910, xvii, 383; 1912, xxii, 301.

forward as a strong argument against the infectiousness of this disease, and Karl Pearson, in fact, at present maintains that phthisis is hereditary and not at all transmissible. Cornet,[25] finding that the rarity of conjugal phthisis contradicts his view of infection, argues that "it is incorrect to regard negative instances in the light of evidence against the contagious character of the disease. The error is the result of an exaggerated estimate of the intimacy of the marital relation." In his opinion the wife, and especially the husband, is apt to be kept away from home as much as two-thirds of the day, and that often man and wife meet each other only at night, and even then they frequently occupy separate rooms through disinclination, impotence, age, occupation, or other causes. This, of course, is a wrong view to take especially by one who, like Cornet, is convinced that infection takes place easily in the factory or mill, where fellow workers hardly ever come very near each other, not to speak of breathing closely one near the other, or kissing each other.

The vast majority of the tuberculous patients reported in this paper have not had separate rooms to sleep in; nay, many slept in the same bed with their partners, and children were born to them during the active, *i. e.*, infectious stages of the disease. Yet the percentage of phthisis in both consorts was only 2.5. Of the 51 widows who lost their husbands through tuberculosis from one to twenty years before this investigation was made, only one showed symptoms and signs suggestive of phthisis.

Our figures are in agreement with those recently published by Ludwig Levy.[26] He investigated 317 married couples who lived in poverty and want; 34 per cent. shared the bed, and a large proportion were dependents. After an analysis of his figures he finds that only in 2.8 per cent. was there probable marital infection. He concludes that marital infection is extremely rare, though it is possible, especially among the poorer strata of population.

The rarity of marital phthisis, despite the exposure, is at present explained more satisfactorily than it was formerly by those who saw in it a proof of the non-communicability of the disease, or lack of opportunities to convey the virus, as Cornet stated. Autopsy findings, as well as the tuberculin test, have shown conclusively that nearly all, or at least 95 per cent. of civilized humanity are infected with tubercle bacilli before reaching adolescence. This is a fact which is no longer questioned by those informed on the recent researches on this subject. The fact that tuberculous infection is not in all cases followed by disease of the lungs or other organs is also well established. But it is not generally known that experimental as well as clinical evidence combine to prove that one infection with tubercle bacilli renders the body immune against renewed

[25] Tuberculosis, American edition, 1904, p. 265.

[26] Statistisches über Tuberkulose der Ehegatten, Beitr. z. Klin. d. Tuberk., 1914, xxxii, 147.

infection with the same virus, just as one attack of typhoid, measles, scarlet fever, syphilis, etc., immunizes against these diseases.

It is thus clear that inasmuch as the healthy consorts of tuberculous individuals have already been infected during childhood, they cannot be reinfected by their tuberculous husbands or wives. That they do not develop phthisis is another matter. In adults individual predisposition apparently counts for more than cohabitation with a consumptive consort. Considering that in human tuberculosis, especially in adults, the consumptive is the main source of infection, it is clear that if the wife of a tuberculous husband or the husband of a tuberculous wife, is close to or intimate with her husband, especially sleeping in the same bed, infection should take place, unless the unaffected partner possesses some immunity. We find, in fact, that gonorrhea is transmitted from husband to wife, or the reverse, in a much higher percentage than from 2.5 to 12 which have been found in phthisis. The same is true of syphilis, unless the apparently healthy partner has been immunized by a previous infection.

There is another class of adults who are greatly exposed to tuberculosis, yet escape the disease in a remarkable manner, thus confirming our findings among married people. I refer to the hospital staffs in sanatoriums and hospitals for consumptives. As was shown in another place by the writer,[27] it is extremely rare that physicians, even laryngologists who are very frequently coughed at by tuberculous patients while doing laryngoscopic work, nurses, attendants, etc., should develop phthisis because of association with sources of infection—tuberculous human beings.

On the other hand we have clinical evidence to the effect that when a non-immunized adult person is brought into contact with tubercle bacilli, or with a person who has tuberculosis, he is soon infected with a very severe form of the disease. This is observed when primitive peoples, like the inhabitants of central Africa, Asia, etc., come in contact with civilized human beings, which is equivalent to tuberculized people in the vast majority of cases, they are soon infected with tuberculosis. It has also been observed that when some of these primitive people are brought to large cities in Europe or America they soon contract tuberculosis and succumb to the disease. In fact, the infection being primary in the adult, it almost invariably produces an acute and fatal form of tuberculosis, as is the case with infants among civilized peoples.

It is different with city dwellers in Europe and America. I have observed that in many cases soon after the death of her husband, the widow who nursed him and underwent great privations, often presents vague symptoms and signs of tuberculosis—she is anemic, debilitated, coughs, and at times expectorates sputum containing

[27] Fishberg, Am. Med., 1915, xxi, 607.

tubercle bacilli. But within a few months she recuperates; the cough ceases, she gains in weight and in general health, so that the original diagnosis of tuberculosis is rendered doubtful. Such cases can be observed in any tuberculosis clinics or sanatorium. It is only necessary to note the fact that in the municipal sanatoriums and hospitals for consumptives it is exceedingly rare to find as patients simultaneously or consecutively both husband and wife. Even after the affected consort succumbs to the disease, and the other consort is treated at the clinic for some time for symptoms suggestive of phthisis, which is not rare, the patients does not need admission to the institution. In fact he or she soon recuperates, and is no more in need of medical treatment.

While examining dependent consumptives in Germany, Levy[28] also found similar conditions. It appears that while previous tuberculous infection immunizes an individual against mild reinfections, it occasionally fails when opportunities for massive infection are presented. The superinfection is, however, in these cases only superficial, and the body rids itself of the bacilli soon after the source of repeated superinfections is removed by death or isolation in an institution of the affected consort.

RÉSUMÉ. The simultaneous or consecutive occurrence of phthisis in husband and wife is extremely rare. In an examination of 170 married couples in which one of the consorts was tuberculous, and who lived under conditions favoring the transmission of the disease in poverty and want and under deleterious hygienic and sanitary surroundings, only 5, or 2.9 per cent., were found in which both the husband and wife were affected with the disease.

Many cases in which both the husband and wife are affected with tuberculosis are met with if carefully looked for. But relatively their number is small, and they appear to be coincidences analogous to cases of conjugal diabetes or cancer (*cancer à deux*), of which there are many cases to be found in medical literature. If direct transmission of tuberculous *disease* from husband to wife, or f om wife to husband, was a frequent occurrence, we would meet with conjugal phthisis as often as we meet with gonorrhea, syphilis, scabies, etc., in both consorts. When it is as rare as conjugal diabetes or cancer, we are justified in concluding that the relatively few cases encountered are mere coincidences. In fact, marital phthisis appears to be less frequent than would be expected considering the great frequency of tuberculosis in the general population, especially in the dependent c'asses.

The rarity of conjugal phthisis cannot be considered as a proof against uncontrovertibly proved transmissibility of *tuberculosis* from the sick to the healthy. It is clearly explained by the facts ascertained recently while making autopsies on persons who suc-

[28] Loc. cit.

cumb to non-tuberculous diseases, and while applying the tuberculin test to apparently healthy individuals. These tests have shown conclusively that practically every person living in a large city has been infected with tubercle bacilli during his or her childhood, though not everyone has become sick with the disease as a result of this infection. It has also been found that tuberculous infection immunizes the individual against exogenic reinfection or super infection with the same virus. For these reasons the unaffected consort of a phthisical person, having been infected with tubercle bacilli during childhood, cannot be reinfected through intimate contact with a phthisical partner. Whether the unaffected consort shall develop phthisis depends on entirely other factors.

The bearings of these findings on our practical application of prophylactic measures in tuberculosis are clear.

THE STATUS OF DIPHTHEROIDS WITH SPECIAL REFERENCE TO HODGKIN'S DISEASE.

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(From the Pathological Laboratory, Roosevelt Hospital, New York, 1914–1916.)

At the present time Hodgkin's disease is quite generally believed to be a specific infection, bacterial or protozoan in origin, but for many years it was a debated question whether it was a malignant new growth or a peculiar form of tuberculosis.

In 1884, Weigert[1] demonstrated in glands of this condition organisms resembling the bacillus of tuberculosis, and in 1898 Sternberg[2] published his extensive monograph, treating Hodgkin's disease as a form of tuberculosis. At this time undoubtedly many cases of tuberculosis, lymphosarcoma, and peculiar hyperplasias were described under this heading, for Sternberg wrote "that many cases of so-called Hodgkin's disease, in which by animal experimentation lymphosarcoma had been ruled out, would be of this tuberculous type." This was based on the finding of tubercle bacilli or their results in glands or in some other part of the body in 15 cases with autopsy. Partly confirming this, Reed,[3] in 1902, injected three animals with gland emulsions; one became tuberculous and the other two showed negative findings. Sternberg,[4] in 1905, realized this dual pathology as coincidental. Why these two conditions

[1] Quoted, Fabian: Centralbl. f. allg. Path. u. Path. Anat., 1911, xxii, 145.
[2] Ztschr., f. Heilkunde, 1898, Bd. xx.
[3] Johns Hopkins Hosp. Rep., 1902.
[4] Path. d. Primärerkrankungen d. Lymphat. u. Hämatopoetischen Apparates, 1905.

were so commonly associated at that time is unexplained, for none of the late reports show this complex. In not one of the glands of a series just reported by the author[5] is the picture suggestive of tuberculosis.

Among the early researches on the bacteriology of Hodgkin's disease in this country were those of White and Proscher.[6 7 8] These writers separately and in collaboration demonstrated spirochetes in large numbers in 4 cases of Hodgkin's disease, in 1 case of leukemia, and in 1 of lymphosarcoma. In this latter case a gland emulsion injected into a guinea-pig, caused in two months, at the site of innoculation an ulcer, with enlarged glands in the groin. Spirochetes were demonstrated in large numbers in both these lesions. Staphylococci and streptococci may give rise to a picture simulating Hodgkin's disease histologically, either by direct infection or as an irritative reaction.

Jacobstal,[9] in 1908, found in one case a granular rod not differentiated from the tubercle bacillus. This was injected into a guinea-pig and caused a transitory lymph-gland enlargement. In 1910 Fränkel and Much[10] reported 10 cases of Hodgkin's disease definitely non-tuberculous, in 9 of which they found by the antiformin treatment of glands, a granular rod non-acid fast. The demonstration was made by Much's modification of Gram's stain. In 5 cases of lymphatic leukemia, by the same method, they found a similar organism. Fränkel[11] in a later communication said these rods were very scanty, sometimes a *three days' search being necessary to find them in tissue.* Bunting in his cultural work refers to this point. Hirschfeld,[12] Rosenfeld,[13] Dietrich,[14] Simonds,[15] and Luce[16] have each reported the finding of granular rods in malignant lymphoma in sections, and by the antiformin method. Sticker and Lowenstein[17] have implanted this tissue in pigs and obtained granulomata with and without tubercle bacilli.

Negri and Mieremet,[18] in 1913, published the morphological and cultural characteristics of a diphtheroid organism similar to that described by Fränkel and Much, obtained from the glands of malignant granuloma. In tissue it appeared as a Gram-positive non-acid-fast granular rod 1.3 x 0.8 m., with rounded ends and central constriction. Cultivation on such media as Bordet, Loeffler, and glycerin-phosphate-potato-agar gave the following forms:

1. Short plump rods, 1 x 0.75 m., with many coccoid forms.
2. Small slender rods, 1.5 to 2 x 0.75 m.

[5] Cunningham: Am. Jour. Med. Sc., 1915, cl, 868.
[6] Jour. Am. Med. Assn., August 13, 1907, xlix.
[7] Ibid.
[8] Ibid., p. 1115.
[9] München. med. Wchnschr., 1910, xiii, No. 1035.
[10] Ibid., p. 685.
[11] Ibid., 1911, Part I, lviii, 1266.
[12] Folia Haemat., 1910, Part I, x, 67.
[13] Berl. klin. Wchnschr., 1911, xlviii, 2196.
[14] Folia Haemat., 1912, xiii, 43.
[15] München. med. Wchnschr., lviii, Part I, 1266.
[16] Ibid.
[17] Centralbl. f. Bact., xv, 267.
[18] Ibid., 1913, lxviii, 292.

3. Small rods 2 to 3 m. long with pale granules. These predominated on old Loeffler media.
4. Granular rods, 5 to 7 m. long and 0.75 to 1.5 m. wide.
5. Involution forms.

In large doses these organisms were non-pathogenic to guinea-pigs and caused only a transitory lymph-gland enlargement in the ape (probably irritative hyperplasia). These writers gave it the name corynebacterium granulomatosis maligni.

Bunting and Yates,[19] in 1913, in a preliminary contribution, reported a pure culture of a Gram-positive, non-acid-fast, pleomorphic diphtheroid organism isolated from 4 cases. In later works[20 21 22 23] complete details of the morphological and cultural characteristics and animal innoculation were described. The organism grew well on Dorset's egg media and glycerin-phosphate-agar incubated for about ten days. Old cultures were transformed into a distinct coccus from which the original bacillus was again obtained on favorable media. This point has been considered by them as quite diagnostic of the Corynebacterium granulomatosis maligni. They have obtained it from all active cases. It is non-pathogenic to guinea-pigs and white rats, and at first did not take hold of the ape well, causing only transitory lymph-gland enlargement. They obtained a more virulent strain which caused the death of an ape in ten weeks, and from which the organism was recovered. Three other animals after repeated injections developed regional lymph-gland enlargement. The pathology of these glands resembled Hodgkin's disease in that there was a pronounced endothelial reaction, fibrosis, and sprinkling of eosinophiles, but there was also an extensive necrosis. These writers believe this picture corresponds to the early histology of Hodgkin's disease, the necrosis depending upon the virulence of the organism. According to the writer's experience this is not the picture early or late, and is not seen in the acutely toxic cases. In human histology necrosis is seen, but is rare and occurs only in small isolated foci.

In the literature there is considerable evidence advanced that the Corynebacterium granulomatosis maligni is the established cause of Hodgkin's disease. There is little if any literature describing these organisms as an accidental factor or as contaminations in the cultural work on Hodgkin's disease. The work I have done was an attempt to confirm the findings of others, and in connection with a study of all the cases that have been at the hospital in the last five years, hoping that something might be accomplished by the use of vaccines. Shortly after the onset of these observations a lymph gland was excised which appeared in the gross like Hodgkin's disease. A diphtheroid organism was isolated from this gland which proved

[19] Arch. Int. Med., 1913, xv, 236.
[20] Jour. Am. Med. Assn., 1913, lxi, 1803.
[21] Ibid., 1914, lxii, 516.
[22] Johns Hopkins Hosp. Bull., 1914, xxv, 173.
[23] Ibid., p. 177.

on section to be tuberculous. Several other glands were cultivated, with the results enumerated below.

The work of Harris and Wade[24] has shown that the diphtheroids are widely disseminated and that many diseases were ascribed to these until the specific cause had later been found. Positive cultures to be of value should have control especially in the cultivation of tissues when the chance of contamination is great. The results of my own observations seem to confirm this. Glands that are not properly cared for may easily be contaminated and harbor the organism which "takes a three days' search to find" to recall the quotation of Fränkel and the reference of Bunting.

If Hodgkin's disease has been produced in the ape with certain cultures then there could be little doubt about the corynebacterium. Necrosis is uncommon in Hodgkin's disease and I dare say never the predominating picture; if such occurs other organisms must be associated. Necrosis is seen in the pyogenic infections, syphilis, tuberculosis, and neoplasms. There is also a reaction in lymph glands due to some type of irritation, showing itself as a pronounced endothelioid hyperplasia, in which the diagnosis without full clinical history is difficult. We know from the work of Blumer[25] that glands of status lymphaticus (bacterial-free?) injected into guinea-pigs will cause lymphatic necrosis, and from the work of Woltman[26] similar effects from foreign sera, etc., may be obtained. In this connection, however, we might say that emulsions of any tissue, bacterial-free, could cause such change a sort of anaphylactic reaction. We cannot say, however, that such reactions are not the results of action of the products of bacteria. Herein lies the etiology of the so-called irritative hyperplasia of lymph glands.

The following grouping is made purely on the grounds of technic in the cultivation. In the first group, glands removed in the operating room were brought to the laboratory in a sterile towel. Here after hastily boiling up the instruments used in gross pathological work some of the glands were mashed, others squeezed and planted on tubes of egg, glycerin-potato-agar and Loeffler. The result of this group is as follows:

Group I. *Case I.* (A) Caseous tuberculous glands. Cultures were made on blood-agar slants. At the end of forty-eight hours slight cloudiness was noted about the tissue and Gram's stain showed a plump bipolar rod with body of organism staining pink. Colonies were very small and tenacious. With Gabbet's stain the polar bodies were more resistant to acid. The organism remained as a bacillus throughout twelve days' observation.

(B) Glands from the opposite side of the neck two weeks later. In four days from glucose-agar slants a large and small Gram-

[24] Jour. Exper. Med., 1915, xxi, 493.
[25] Quoting Flexner, Johns Hopkins Hosp. Bull., 1903, xiv, 275.
[26] Jour. Exper. Med., 1905, vii, 119.

positive bacillus and coccus were isolated. Transplants gave a good growth of a Gram-positive pleomorphic rod. On Loeffler forms appeared more slender. Morphologically it is different from that isolated from the opposite side of the neck.

Case II. Caseous tuberculous glands. Cultures made on glucose serum agar and blood agar. In six days from serum-glucose-agar a short Gram-positive rod, bipolar, was isolated. Many coccoid forms were seen. Cultures eleven days old presented many clubbed forms. The younger cultures were similar to IA, but the older cultures showed many involution forms. One tube remained sterile.

Case III. Tuberculous lymph gland. Cultures made on ascitic glucose agar. Two tubes gave a pure culture of Staphylococcus albus and one tube a mixed culture of a short Gram-positive bacillus and coccus. It was impossible to isolate the bacillus, but the few seen showed no pleomorphicity.

Case IV. Subleukemic lymphadenosis. Clinically and pathologically this was a very interesting case, but far from a typical Hodgkin's.[27] A gland was removed from the axilla and cultivated by Dr. Warren. A Gram-positive pleomorphic rod was isolated which became coccoid. It was transformed into a bacillus and recognized by Bunting as a typical Bacillus hodgkini. Some of the other organisms isolated are very similar to this strain and have the same tendency to become coccoid, and these from glands definitely tuberculous.

Case V. Hodgkin's disease. Five tubes were innoculated and three gave a large Gram-positive coccus.

(*a*) Egg tube. Diphtheroid bacillus arranged in parallels, Gram-positive with body staining pink. It appeared first as a short bacillus but with subsequent cultivation on Loeffler the forms appeared longer and more slender. It remained as a bacillus throughout three weeks' observation. The young transplants appear very short, with rounded ends, and became distinctly pleomorphic.

(*b*) Glycerin-potato-agar. A short Gram-positive digastric bacillus was obtained. After seventy-two hours many small coccoid forms were seen. It later became contaminated.

Case VI. Large round-cell sarcoma, primary mediastinal. A supraclavicular gland was excised for diagnosis and cultivated on glycerin-potato-agar and egg media. From one tube was obtained a short Gram-positive bipolar rod with central constriction and from another a Gram-positive coccobacillus. On Loeffler the pleomorphicity of the former was better made out and the forms were more slender. After several days' growth many cocci and coccoid forms were seen. Several other tuberculous glands were cultivated and a large coccus was obtained.

[27] Warren: Proc. New York Path. Soc., 1915, xv, No. 142.

While this work was in progress approximately 225 cultures were made in the wards, operating room, and laboratory, and diphtheroids were isolated several times. None, however, came from the operating-room cultures. One was from a culture taken from the heart's blood in the morgue. Dr. Warren called attention to the fact that there had been several periods at the hospital when diphtheroids were frequent contaminators in blood cultures. One of these periods followed shortly and several cultures after four to five days presented diphtheroids in the broth. We felt that our technic could be improved, so subsequent cultures were made in the Syms operating room carrying out aseptic technic to the minutest detail, with the following results:

GROUP II. Two cases of Hodgkin's disease, one cervical the other axillary; both showed rapid enlargement in the past few months. Glands from both these cases were cultivated on several tubes of egg and glycerin-potato-agar and remained sterile at the end of two months.

Four cases of tuberculosis:

(A) Soft caseous gland; all tubes gave a Staphylococcus pyogenes albus.

(B) Chronic tuberculous lymphadenitis; all tubes sterile at the end of month.

(C) Retroperitoneal gland (tuberculosis of ileum). Pure culture of Bacillus coli in two tubes; one tube remained sterile for three weeks.

(D) Endothelioid tuberculosis. Four tubes remained sterile. One case of chronic cervical lymphadenitis, unclassified, but with a specific history, gave in two tubes a slowly growing streptococcus.

SUMMARY AND CONCLUSIONS. All these organisms may be placed in the diphtheroid group, and only on morphological grounds am I able to say that many of them are of different strains. The organisms which were isolated from glands of Hodgkin's disease, however, are very similar if not identical with those from the tuberculous glands. In Case I, cultures from glands on both sides of the neck, two weeks apart, gave somewhat different organisms, while that described from IA appeared like the organism isolated from Case II. In some instances the diphtheroids were primarily associated with cocci which later overgrew them.

It is reasonable to suppose that glands draining such places as the mouth, throat, and tonsils should harbor such organisms as are commonly found in these portals. With the evidence at hand, however, the occurrence of them in the laboratory, in blood cultures (appearing rather late), in the heart's blood at the morgue, in ascitic fluid, and in a series of gland cultures of questionable technic, and not in a series where technic is definitely controlled, I am led to believe that we are dealing with organisms whose natural habitat is the laboratory. The series is, however, too small to make

a positive statement, but I do not believe the organism heretofore described bears any relation to the cause of Hodgkin's disease.

I wish to acknowledge with thanks the courtesy of the attending staff in supplying me with the material and the suggestions and coöperation of Dr. Warren.

SOME PHYSIOLOGICAL EFFECTS OF VARIOUS ATMOSPHERIC CONDITIONS.[1]

By James Alexander Miller, A.M., M.D.,
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Atmospheric environment is an interesting and important factor in many medical problems in which no group of physicians is more directly interested than are the members of the American Climatological and Clinical Association, and, moreover, no one in this country has contributed more than they to the advancement of this phase of medical knowledge.

It is for this reason and also as a result of my own recent experience for three years in the work of the New York State Commission on Ventilation that this topic has been chosen for presentation on this occasion.

It is my purpose to approach the subject more from the physiological point of view in the hope that by a consideration of certain fundamental principles a clearer vision may be afforded of the problems involved in the effect which atmospheric conditions exert upon the comfort and efficiency of mankind as well as of the role they may play in the causation, prevention, and treatment of disease.

The respiratory functions of air focussed the attention of physiologists for generations, in fact, until very recent years. Consequently its effect upon the human body was interpreted solely in respiratory terms and rules of hygiene were formulated upon this basis. Withindoors inadequate ventilation was gauged in terms of deficient oxygen or of excess of carbon dioxide, or later of the presence of certain volatile poisons in the air that was breathed. Outdoors the general effect in health and disease produced by variations in climate or of its temporary representative, the weather, was also ascribed solely to their influence upon the air we breathe. To the truthful part of this hypothesis we all pay fitting tribute in the joy of the full deep breath upon a fine, crisp morning.

Under the lead of Pettenkofer[2] the CO_2 content of the air was for

[1] President's address at the meeting of the American Climatological and Clinical Association, Washington, May 9 to 11, 1916.

[2] Liebig's Annalen, 1862–1863, Suppl., ii, 1.

many years taken as the indicator of hygienic fitness until Haldane[3] showed that the alveolar CO_2 content of the air does not vary even when it is largely in excess of the atmospheric air, and he and others have demonstrated the lack of discomfort or other symptoms until the percentage of CO_2 reaches a point many times in excess of the range of possibility under any but experimental conditions. The same may be said of the effect of diminution of oxygen within any ordinary or probable limits.

In 1887 the researches of Brown-Séquard[4] claiming the existence of volatile organic poisons in expired air and explaining the symptoms of exposure to vitiated air upon this basis claimed wide attention. Although very recently Rosenau and Amoss[5] have reported the presence in expired air of substances which cause an anaphylactic reaction in animals no other observers have been able to corroborate the results or conclusions of Brown-Séquard.

Other substances in the air, such as dust, bacteria, and odors, are recognized as playing a part in its hygienic properties, but recent investigations appear to demonstrate that under ordinary conditions they are not factors of sufficient importance to materially affect health.

In general it may be accepted that the chemical or bacterial content of the air within any likely degree of variation is not of material moment either hygienically or physiologically.

The retention of CO_2 determinations as a gauge of the amount of air change in indoor conditions is the only remnant of the era of chemical standards for determining the hygienic condition of the air, and this gauge so used has no reference to the CO_2 content itself as an important physiological factor.

Researches of the last decade have all led to the appreciation of the physical as opposed to the chemical features of the air as the important physiological factors. It is the reaction of the body to its environment through the skin surface rather than through the respiratory organs which is now recognized as of fundamental physiological importance. This may be expressed as the ventilating function of the skin, and the problems involved are largely those of the satisfactory heat regulation of the body.

Hermans[6] in 1883 was the first to call attention to this important fact, but it was brilliant experiments of Paul[7] in Flugge's laboratory in 1905 that first riveted the attention of the scientific world upon this aspect of the problem. In cabinet experiments he adequately explained all of the symptoms caused by vitiated atmosphere in terms of temperature, humidity, and air movement. Since then

[3] Haldane, Jour. Path. and Bacteriol., 1893, I, 168, 318.
[4] Compt. rend. Soc. de biol., 1887, s. 8, lv, 814.
[5] Jour. Med. Research, 1911, xxv, 35.
[6] Arch. f. Hyg., 1883, i, 5.
[7] Ztschr. f. Hyg. u. Infectious-krankh., 1905, v, 405.

his results have been amply confirmed, notably by Rubner,[8] Flugge,[9] Haldane[10], Leonard Hill.[11]

Adequate heat regulation of the body depends largely upon the capacity for proper heat elimination, which is accomplished in three principal ways, which vary in their relative importance according to the varying external conditions.

1. Evaporation of water from lung and skin surfaces.
2. Direct conduction by contact with a cooler medium.
3. Direct radiation to a cooler distant surface.

1. Evaporation. This takes place continuously from lung surfaces, to a greater or less extent from skin surfaces. Its rate depends upon (*a*) air temperature, (*b*) humidity, and (*c*) velocity of air movement.

Temperature and air movement are of primary importance in skin evaporation and of only minor importance for the lungs. Humidity affects both kinds of evaporation, but in the skin it is the relative humidity which is of primary importance while in the lungs it is the actual amount of moisture that determines the rate of evaporation.

2. Direct Conduction. In contact with the surrounding air the rate of heat elimination from the skin by conduction depends upon the following properties of the air: (*a*) temperature, (*b*) thermal capacity, (*c*) thermal conductivity, and (*d*) velocity of movement.

The thermal capacity and conductivity depend upon (*a*) the density (pressure), (*b*) the humidity, and (*c*) the temperature.

3. Direct Radiation. This is a factor of minor importance, but may heed recognition in the association with the other two more important conditions.

Taking, therefore, these more important conditions together, that is, evaporation and conduction, we find that the various factors reduce themselves finally to four: namely, temperature, humidity, barometric pressure, and velocity of air movement. The interrelationships of these factors are very complex, so that no simple statement of the exact physiological effect of each is possible. For example, it is a well-known experience that high temperature with low humidity is often more comfortable than lower ones with high humidities. Here the effect of humidity upon evaporation is the predominating factor. On the other hand, low temperature with low humidity may be quite bearable, while a higher temperature associated with dampness may be distinctly chilling. Here it is the relation of the humidity to direct conduction that predominates.

In the consideration of the concrete physiological problems which I now propose the factors of the temperature, humidity, and

[8] Arch. f. Hyg., 1897, xxiv, 1.
[9] Ztschr. f. Hyg., 1905, xlix, 363.
[10] Jour. Path. and Bacteriol., 1893, i, 168, 318.
[11] Smithsonian Miscellaneous Collections, 1913, lx, No. 23.

movement of the air will be those mainly considered as the additional factor of barometric pressure will lead us a little too far afield.

Effect upon Comfort. Analysis of much that has been said and written of the physical effects of air conditions, both within-doors and outdoors, reveals the fact that the opinions expressed are very largely based upon sensation of comfort or discomfort, these are nothing more or less than personal impressions and lack scientific definiteness.

In extreme conditions of heat, humidity, and air stagnation there of course results certain definite symptoms, easily recognizable, and, within certain limits, common to all animal life. A sense of oppression, headache, dizziness, faintness, and nausea are symptoms with which we are all familiar. The fundamental experiments of Paul and others already cited were based upon the causation and relief of such symptoms under varying atmospheric conditions of a physical nature. Such effects are not debatable. When, however, we consider the less extreme conditions the situation is different. There are no definite concrete symptoms, and impressions are very variable.

Haldane,[12] who has done some of the most exact work in this field, concludes, from numerous experiments, that the combination of temperature and humidity records, as shown by the wet bulb thermometer, is the only reliable index, and places the maximum comfort for men at 68 wet bulb while actual symptoms occur at 78 wet bulb.

Professor Afflick[13] in studies of gymnasium ventilation found that 55° to 63° F. dry was never uncomfortable, but that when humidity was considered the individual variations were so great that definite conclusions were not possible. He found that opinions of comfort varied all the way from 29 per cent. to 77 per cent. relative humidity.

Hickor[14] also in studies of gymnasium ventilation found very great variation, but concluded that 58° to 64° (dry bulb) is the best for gymnasium comfort and that variations between 22 per cent. and 65 per cent. relative humidity had no effect on comfort.

The New York State Ventilation Commission[15] found in its cabinet experiments that the subjects were somewhat more comfortable at a temperature of 68° F., but the difference experienced between this and much lower or much higher temperature was not as marked as would have been expected. The same results held good in varying degrees of humidity. One interesting finding was a decrease of appetite in stagnant air and compared with the free admission of fresh air.

In its schoolroom experiments with recirculated air there was no marked difference in the comfort votes of teachers and other obser-

[12] Jour. Hyg., 1905, v, 494.
[13] Am. Physical Educ. Review, 1912, xvii.
[14] Thesis, Internat. Y. M. C. A. College, Springfield, Mass., 1914.
[15] Preliminary Report, Am. Public Health Jour., 1915.

vers between these two conditions, which coincides with the observations of Bass[16] in Minneapolis.

There is a noticable lack of data in the literature as to the comfort effects of low temperature combined with varying degrees of humidity and air movement. It is generally recognized, however, that this is susceptible to personal idiosyncrasies, as many or more than at the higher temperatures, and experience in inuring patients to cold air, often at first strongly contrary to their sensation of comfort, demonstrates how large a role habit plays in this matter.

Many observers have noted also that feelings of comfort often depend upon contrasts. On a cold day a room at 50° F. might seem warm and comfortable while in warmer weather the same temperature might well be uncomfortably chilly, all of which shows our powers of adaptation, but does not increase our confidence in comfort sensation as an index of physical condition. At present, however, they constitute the basis of much of our medical opinion and clinical advice in these matters.

Effect Upon Physical Efficiency. Some evidence is at hand concerning the effect of high temperature and humidity upon working efficiency. Very little exists regarding the similar effects of low temperatures and humidities. Haldane[17] found that when at work, subjects were unaffected at 71° to 72° F. dry, or 64° to 65° wet bulb, but that actual disabling symptoms occurred at 78° wet bulb or above. His observations coincide with others and may be accepted as a present standard.

In the Ventilation Commission experiments it was found that body temperature and pulse rate were raised at 86°, but lowered at 68° and below, and the Crampton index of vasomotor tone was lowered by temperatures of 77° and 86°, especially when associated with high humidities. Systolic blood-pressure was somewhat higher in the lower temperatures. Also 37 per cent. more work in dumb-bell lifting was accomplished at 68° with 55 per cent. humidity than at temperature of 77° and 86° and somewhat higher humidities. In another series 15 per cent. more physical work was done at 68 and 50 per cent. than at 75° F. with the same humidity.

These results with only moderately high temperatures are interesting and of more practical value than the majority of similar experimentd in which very high temperatures are employed, showing, as they do, that degrees of moderate heat which are often experienced under ordinary conditions of life are not without measurable physiological effect.

Efforts to obtain more exact physiological indices of the response to temperature than the usual ones employed of body temperature,

[16] Am. Soc. Heat. and Vent. Engineers, 1913, xxix, 328; ibid., 1915, xxi, 109.
[17] Jour. Hyg., 1905, v, 494.

pulse rate and blood-pressure, were made. Studies with this end in view were made by Professor Frederic S. Lee upon the duration of digestion, the alveolar CO_2, the oxyhemoglobin in the blood, the rate of pulse recovery, the size of the dead space in the lung, the specific gravity and freezing-point of the urine, and the excretion of creatinin, but all failed to show any definite changes as a result of various atmospheric conditions.

One of the most interesting contributions to this general subject is Ellsworth Huntington's[18] recent book. In support of his main thesis, namely, that conditions of weather and of climate play a dominating part in the development of peoples as well as of individuals, in those characteristics which go to make up the general sum of what we call civilization, this interesting writer makes use of carefully controlled observations and statistics upon the working efficiency of several large groups of workmen under various conditions.

The groups observed in these studies were operators in three factories in Connecticut, Bridgeport, New Haven, and New Britain respectively, girls in a tobacco factory in Winston-Salem, North Carolina; operators in two cotton mills in South Carolina and in two others in Georgia; a group of cigarmakers in Jacksonville and another in Tampa, Florida, and, lastly, carpenters in Jacksonville, Florida.

From all of these diverse sources he obtains remarkably harmonious results and reaches conclusions which may be summarized as follows:

1. There exists a regular seasonal variation in physical efficiency which in this climate is shown by two maximum waves, one occurring in the spring, May and early June, and the other in the autumn, October and early November, with a corresponding depression in midwinter and midsummer.

2. The main factor in the seasonal variation is temperature. The percentage of sunshine and relative humidity are minor factors of some, but relatively slight importance.

3. Extremes of temperature whether high or low are detrimental, and there exists an optimum temperature for physical efficiency, which Huntington's statistics shows to be 60° F.

4. A change of temperature, if not too great, is more stimulating to working efficiency than uniformity, and a fall of temperature has more effect than a rise. A fall of 4° to 7° F. is everywhere stimulating.

5. Efficiency is more marked at the end of a storm and least so on very clear days. Each storm with its changing skies, varying humidities, and slow rise and rapid fall of temperature is a stimulant and raises efficiency.

[18] Civilization and Climate, New Haven, 1915.

6. The ideal climate from the stand-point of efficiency is one in which the temperature range is between 38° and 65° F., in which the humidity is uniformly neither very high nor very low, and in which there occur frequent but moderate variations in temperature from day to day, interspersed with a considerable number of cyclonic storms.

These opinions which I have thus briefly summarized when supported by the data and reasoning which Professor Huntington presents, deserve careful thought and critical study at the hands of the clinicians and especially of climatologists.

Effects upon Mental Efficiency. Of the influence of atmospheric conditions upon effective mental effort much has been claimed from time to time, but little has been proved.

Lehmann and Pederson[19] conducted a long series of experiments upon school children which included addition and memory tests as well as strength tests with the dynometer. They found a seasonal variation in both the mental and physical tests very similar to those of Huntington, with an optimum temperature for both mental and physical efficiency which varied greatly between individuals. In general the optimum for mental work was found to be much lower than that for muscular exertion.

Huntington[20] made careful observations of the relation between mental efficiency and weather and seasonal changes, as evidenced by the study marks of cadets at West Point and Annapolis over several years. He found a seasonal variation of mental efficieney, evidenced by two maximum waves each year. These waves occurred in March and in November or early December, that is, at seasons when the temperature was dictinctly lower than he found to be desirable for maximum physical efficiency.

He concludes that a temperature of about 40° F. is the optimum for mental effort.

Very extensive experimental studies of mental work in various atmospheric environments have been made by the New York State Ventilation Commission. The results of these are soon to be reported by Professor E. L. Thorndike of the commission. In general, however, they showed very little effect that could be demonstrated by the most scientific psychological methods of investigation. The most striking result was a lack of inclination for mental work in high temperature, such as 86° F. with high humidity (80 per cent. rel.), but even here this could be overcome by the application of some increased incentive to work.

General experience with outdoor schools leads to the impression that conditions there make for increased mental capacity. If this be true, as seems likely, it would be a rational explanation to ascribe this benefit to the much lower temperatures which obtain in these class

[19] Arch. f. d. ges. Psychol., 1907, x, 1.

[20] Loc. cit., p. 77.

rooms. With the large number of outdoor schools there now exists so much available material for statistical investigation that it is to be hoped that some well-conducted and carefully controlled studies of this subject will be forthcoming. It would be specially interesting and instructive to know more of the actual effects of the very low temperatures often noted in these classes, for they are far below the optimum temperature for mental work suggested by Huntington and by Lehmann and Pederson.

Clinical Features. There are many interesting and important applications for the physiological problem which we have thus briefly considered. At the present time I will attempt to discuss only two of the more important of these, namely, "Ventilation" and the "Fresh Air Treatment" of disease. The first concerns us chiefly in the conservation of health and the prevention of disease, while the latter is a generally accepted and invaluable therapeutic agent.

If we are to adapt the knowledge obtained from physiological research to these practical problems it is evident that the chief emphasis is to be placed upon atmospheric temperature.

Our standards have been largely those of individual comfort which we have seen to be susceptible to very considerable variation and to depend very largely upon the facility of adaptation to the body environment.

There has been a considerable amount of loose medical thinking upon this subject and we are sorely in need of more scientific data based upon accurately observed clinical phenomena. Fully as I appreciate their shortcomings, I am not entirely in sympathy with the popular denunciations of ventilating engineers and their artificial systems.

The fault appears to me to be more one of our standards, for I I am convinced that by a rational combination of open windows, a good heating plant, and a proper air exhaust system when necessary that practically any desired condition of indoor air may be obtained. The two chief faults appear to be too high temperature and too little variation in temperature.

The results of recent studies all appear to point in this direction, and were we able to agree upon new standards embodying the correction of these faults there is little doubt of the availability of the physical means to carry them out. Any system of ventilation, however, whether natural or artificial, stands or falls by the intelligence with which it is operated, which presupposes a knowledge of the desired ends to be obtained. There would seem to be needed, therefore, a wider appreciation of the physiological importance of cooler and more variable temperatures as the prime factors in proper ventilation to which all others, including even humidity, are secondary.

When we turn to the fresh air treatment of disease it would seem as though here also we have much to learn from physiological studies. If there is advantage to be desired from open air, as it

happens to be, it would seem as though there might be still more to be gained from skilful modification of these air conditions to meet the indications arising in various diseases or in individual cases. This would involve not only a more general knowledge of what is known of the physiological effects of various atmospheric conditions, but, what is even more needed, a systematic attempt to extend this knowledge by a correlation of the physical, physiological, and clinical factors involved. This can come only through close study of the reaction of various types of disease to the atmospheric environment, and entails the use of accurate records of temperature, humidity, barometric pressure, and air movement as a part of regular clinical procedure.

It would seem, for example, that valuable use might be made of Huntington's suggestion of the effects of temperature change when the weather does not happen to supply it adequately or that the ill effects of certain seasons or weathers might be modified and the good effects of others artificially reproduced by the intelligent use of means easily at our command.

The great variation in medical opinion upon these matters demonstrates the fact that our clinical knowledge is still imperfect and inexact and that standards of procedure in various diseased conditions must be supplied by careful clinical study and experimentation.

My suggestion, therefore, is that by breaking up into its component parts the heterogeneous mass of physical and physiological factors, now included in the term "Fresh Air Treatment," and studying the effect of each, we may be able to reach a point where the proper atmospheric conditions may be intelligently applied to the suitable case of disease, and results obtained which would be far more satisfactory than at present, both from a clinical and scientific point of view.

I believe that we can confidently look to the members of the Climatological and Clinical Association to take the lead in this direction.

OBSERVATIONS UPON A CASE OF EXTREME ACIDOSIS OCCURRING IN A MAN WITH BILATERAL CYSTIC KIDNEYS.

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We have recently had an opportunity to make observations of the various factors of acidosis in a case of bilateral cystic kidneys

with terminal uremia and accompanied by extreme dyspnea. These findings seemed sufficiently remarkable to us to be worthy of recording.[1]

The clinical history was as follows:

S. C., male, aged forty-six years; single; colored; bricklayer. Hospital numbers 207051, 207864, 208858; entered the medical service of the hospital February 29, 1916.

Family History. Unimportant.

Past History. Typhoid fever eight years ago; gonorrhea three times, the last ten years ago. No history of syphilis.

Habits. Good. No alcohol or tobacco. Bowels always very constipated.

Present Illness. During the last five years, for about two months in the middle of each winter, he has been bothered with certain gastro-intestinal symptoms, flatulence, abdominal distress, vomiting, anorexia, and loss of weight and strength. With these symptoms he has in addition occasionally had some edema of the face, hands, and feet and a moderate polyuria. He was sent to the hospital from the out-patient department in order that a lumbar puncture might be done. In the out-patient department bismuth roentgen rays had been taken which showed nothing abnormal save a rather active hypertonic stomach and some delay in the passage of the bismuth mass in the lower portion of the descending colon.

Physical Examination was essentially negative. Pulse, temperature, and respiration were normal. The blood-pressure was 135 mms. systolic and 70 mms. diastolic.

Laboratory Examinations. The urine showed the slightest possible trace of albumin; in other respects it was normal. No casts were found. The blood: Hemoglobin 80 per cent., white count 7200; the smear was not remarkable. The Wassermann test was negative. The spinal fluid was clear; there was no excess of cells; the gold chloride and Wassermann tests were negative.

The patient was discharged March 1, 1916. He entered the hospital again April 17, 1916, having failed to improve; he came in for further study on the advice of his own physician. He remained in the medical wards until May 16, and during that time he developed and recovered from an unexplained fever of twelve days' duration.

Physical examination at this second entry showed him much emaciated. A systolic murmur was heard over the apex of the heart; a mass was felt in the right upper quadrant of the abdomen which was thought to be kidney. It was felt by several observers. There was no edema.

The urine was examined repeatedly during this stay in the hospital and was always of low specific gravity, sometimes showing

[1] We are indebted to Dr. W. H. Smith for the opportunity to study this case.

a slight trace of albumin, sometimes none. No casts were ever found. The blood even at the height of his febrile attack showed no leukocytosis.

The blood-pressure was never higher than 135 mms. systolic, and at the height of his febrile attack was only 100 mms.

The renal function (sulphonephenolphthalein excretion) was determined on several occasions. On April 1 it was less than 5 per cent. in two hours. It was the same on April 25, and on May 4 only a trace was eliminated in two hours.

The non-protein nitrogen of the blood was 97 mgms. per 100 c.c. April 20 and 71 mgms. May 4.

May 16 he was discharged, slightly improved. The diagnosis was in doubt. It was thought he must be in chronic uremia, and amyloid or cystic disease of the kidneys was thought more likely than a real nephritis. The occurrence of fever and the fact that the patient stated he had previously had fever with his attacks suggested a possible etiology for amyloid disease.

June 9, 1916, he again entered the hospital, this time on the surgical side, with a septic hand which he had had for two weeks. After leaving the hospital the last time he had felt better until the sepsis had begun.

His hand was poulticed and things were going along smoothly until suddenly, on the morning of June 12, he began to have a most extraordinary hyperpnea. He was seen by members of the medical staff in consultation and was transferred to the medical service. At this time, noon, June 12, he gave the impression of a man who has just done the most violent muscular work. Each respiration was maximal and all the accessory muscles were working. The rate was about 25. The patient was perfectly conscious, and stated that he felt as though he had been running. There was no orthopnea and no Cheyne-Stokes periodicity to the breathing. A number of special tests were made at this time which will be discussed later. These showed that an extreme acidosis was present.

The hyperpnea continued during the day, and in the evening the administration of alkali was begun. Sodium bicarbonate, 10 grams every four hours by rectum, was given until 2 A.M., June 14. After that 20 grams was given by stomach tube every eight hours. This was continued until death.

On the morning of June 13 the breathing was still labored, but not nearly so much so as on the day before. The rate was 20; during the extreme hyperpnea it reached 50. The patient was semicomatose. He passed very little urine, and that only after catheterization.

June 14 he was a little brighter. He would answer questions. His speech was thick but not aphasic. There was much less hyperpnea. The accessory muscles were not employed. This day the general character of the breathing was deep and sighing, much like

that of diabetic coma. The rate was 18. In the afternoon he gradually lapsed again into coma. His mouth became very dry. The temperature rose rapidly to 105°. He developed twitchings of the muscles about the mouth. The respirations became gradually less and less stertorous, the rate falling to 10, then 8, then 3, etc., finally ceasing altogether at 11.05 P.M., June 14. The cardiac action was good up to the time the breathing stopped, and continued several minutes thereafter. It was clearly a death from respiratory, not circulatory, failure. A blood culture showed a terminal streptococcus septicemia.

The urine failed to show any diacetic acid or acetone at any time. A slight trace of albumin was present, but no casts were found.

The blood-pressure as before was 135 mms. systolic, 70 mms. diastolic.

AUTOPSY. The kidneys were about three times the normal size, the right being slightly greater than the left. The left kidney substance was practically replaced by mutiple cysts varying in size from that of a pea to about 2 cms. in diameter, and containing fluid varying from a clear, watery substance to light brown, dark brown to black, thick material. The contents of the cysts gave a foul odor. They were not connected with the renal pelvis, which was atrophic, as was also the ureter.

The right kidney showed similar cysts, but smaller and fewer in number. There were small islands of renal tissue between the cysts, but the color was pale and the consistency increased. This renal pelvis was slightly atrophic.

The right lobe of the liver at the rounded, thickened portion showed a few subcapsular cysts containing clear fluid, and deep in the tissue in this region were several cysts, varying in size up to 1.5 cms.

The lungs showed pneumonia at the bases and the right lung showed consolidation extending well up on the posterior surface.

The autopsy (including the head) in other respects showed nothing noteworthy.

SPECIAL STUDIES. This case presented an unusual opportunity for study, so the following investigations were carried out:

Respiration Experiment. June 12, at noon, at the height of the hyperpnea and before any alkali had been given, a five-minute period on the Benedict apparatus (mouthpiece, spirometer type) was secured. This experiment gave these results:

Respiration rate	22.5	
Volume per respiration	2440.0	c.c.
Total ventilation per minute	55.0	liters
Total ventilation per minute reduced to 0° and 760 mms.	50.6	liters
CO_2 in expired air	0.71	per cent.
CO_2 eliminated per minute	360.0	c.c.
O_2 eliminated per minute	not obtained	

Alveolar carbon dioxide tension was determined June 12, just before the respiration experiment, by the Plesch-Higgens method. It was 0.9 per cent. or 6.4 mms. of mercury.

The index of urea excretion was determined by the routine described by McLean[2] on the afternoon of June 12 (before any alkali had been given). The diet for the preceding forty-eight hours had been free from meat, fish, and salt. The following data were obtained:

Urea in the blood	332.0	mgms. per 100 c.c.
Urea in the urine	0.449	gm. in 72 minutes.
Volume of urine	55.0	c.c. in 72 minutes.
Patient's weight	60.0	kg.
Index of urea excretion[3]	34.8	

The same urine showed NH_3 0.0104 gms. in seventy-two minutes, or 0.208 gms. in twenty-four hours. No diacetic acid or acetone.

The Alkali Tolerance. The urine remained acid to litmus up until death in spite of the administration of large amounts of sodium bicarbonate as outlined in the history. (Total 110 grams in two days.)

The carbon dioxide capacity of the plasma was determined on several occasions by the method of Van Slyke. At 3.16 P.M., June 12, before alkali administration had been begun the volume of CO_2 bound by 100 c.c. of plasma was 12.1 c.c., equivalent to an alveolar air CO_2 tension of 8.35 mms., Hg.

June 13, at 12.30 P.M., after the patient had been on sodium bicarbonate 10 gms. every four hours for eighteen hours, it was 20.1 c.c., equivalent to a tension of 13.87 mms. Hg. June 14, at 11 A.M., it was 37.4 c.c., or 25.8 mms. Hg.

The renal function (sulphonephenolphthalein elimination) June 12 was zero in three hours.

The acid ammonia ratio, which was determined for us by Dr. W. W. Palmer by the method described by Palmer and Henderson[4] was 1.00. This, Dr. Palmer writes, is to be considered a high normal. The urine for this test was obtained June 12 before any alkali had been given.

The non-protein nitrogen of the blood (Folin method) was 189 mgms. per 100 c.c. June 12.

The blood-sugar (Benedict's method) on June 12 was 0.22 per cent.

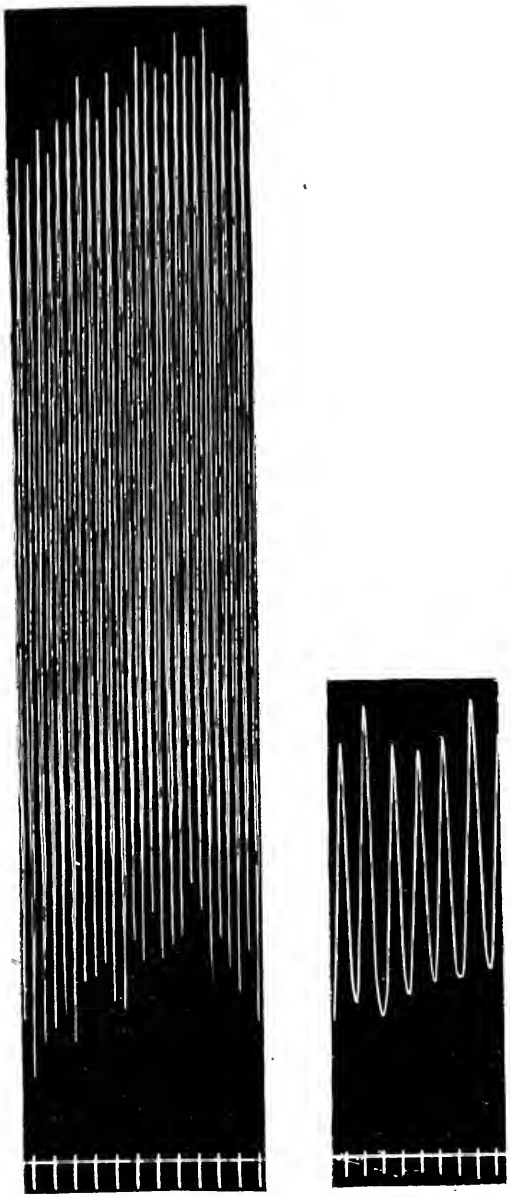
The phosphorous content of the serum Dr. John Howland was good enough to determine for us. Dr. Howland writes: "The

[2] Jour. Am. Med. Assn., 1916, lxvi, 415.

[3] Index of Urea Excretion =

$$\frac{\text{Grams urea in 24 hrs.} \times \sqrt{\text{grams urea per liter urine}} \times 8.96}{\text{Weight in kilo} \times (\text{grams urea per liter of blood})^2}$$

[4] Arch. Int. Med., 1915, xvi, 109.



The patient's respiratory curve, June 12, at the height of the hyperpnea on the left. That of a normal man of approximately the same weight on the right. Both tracings taken with the Benedict apparatus. The time intervals are five seconds. Both subjects lay flat on the back while breathing into the apparatus. A mouth-piece was used in each case.

phosphorus content of the serum . . . . in the form of inorganic phosphates was 18 mgm. per 100 c.c. The normal varies between 1 and 3.5; you see, therefore, the very great excess. This is nearly as high as we have ever found it; up to the present time (June 19, 1916) 23 mgm. per 100 c.c. has been the highest."

The calcium content of the blood Dr. Howland also kindly determined, and writes as follows: "The calcium content of the patient's blood that you were good enough to send me was 3 mgms. per 100 c.c. This is less than one-third the normal, the normals running from 10 to 11. This diminution of the calcium we have found to be almost as regular as the increase of phosphate."

Discussion. This case is interesting in that it presents one of the most intense acidoses ever reported in uremia. Peabody reports one case of uremia having a CO_2 tension (Plesch Higgens) of 6 mms., and another with a tension of 19.1 mms.[5] As a rule, however, in uremia the CO_2 tension rarely falls below 25 mms. even in the terminal stages. Of course, in diabetes CO_2 tension of 6 mms. or less are not uncommon.

The severity of the hyperpnea is extraordinary. The minute volume of 50 liters is easily ten times the normal resting ventilation, and the volume per respiration of 2440 c.c. is at least 60 per cent. of his probable vital capacity, whereas the normal resting tidal respiration is about 5 per cent. of the vital capacity. This ventilation is greater than that of one of us (J. H. M.), who is about the same size as the patient, when he was doing about 800 kg. meters of work per minute on a bicycle ergometer.[6] Under these circumstances the normal subjects CO_2 elimination was over a liter a minute instead of 360 c.c., as in the case of this patient.

That the hyperpnea was in large part due to the acidosis seems probable because of the distinct improvement secured by giving alkali. This improvement was in the respiration only. Although the acidosis was diminished by giving alkali, as proved by the rise in blood CO_2, the patient's general condition grew progressively worse.

That the acidosis was one of retention rather than of production is suggested by low renal function tests, and the low index of urea excretion together with the high phosphates and non-protein nitrogen of the blood and the autopsy finding of almost total absence of normal renal tissue.

That there had been a tremendous withdrawal of base from the body is shown by the high alkali tolerance. In this connection it is interesting to note a striking difference between this case and the cases of chronic glomerular nephritis studied by Palmer, in that here the utilization of NH_3 to neutralize acid, as shown by the acid

[5] Arch. Int. Med., 1915, xvi, 955.
[6] Means and Newburgh: Jour. Pharmacol., and Exper. Therap., 1915, vii, 449.

ammonia ratio, is normal, whereas often in chronic nephritis there is a definite inability to utilize ammonia.[7]

The fact that a severe acidosis is present, that the acid ammonia ratio is normal, and that nevertheless the total NH_3 excretion is not increased shows very clearly that the excretion of acid is greatly impaired.

The clinical picture is similar to that commonly found in bilateral cystic disease of the kidneys. Pain and digestive symptoms are common at the onset. Edema is rare. Terminal uremia is usual. The urine is usually increased in amount, with little or no albumin, low gravity, and no casts. The blood-pressure often shows no elevation.

THE INVASIVE QUALITY OF THE STREPTOCOCCI IN THE LIVING ANIMAL.[1]

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Invasion, virulence, and pathogenicity as well as resistance and susceptibility are all relative terms and must be considered from the point of view of the animal body as well as the bacteria themselves. This is generally recognized but is not constantly remembered.

The streptococci have primarily high invasive powers. By this I mean that they are capable of entering the animal body under a wide variety of conditions. It is only within the last few years that this has been broadly recognized. The Bacillus coli formerly was the organism found as the chief secondary invader. In autopsy bacteriology the colon bacillus is frequently reported as the common bacterium invading after death, and in studies of peritoneal and other fluids the same organism was found practically to the exclusion of all others. More careful technic has, however, definitely shown that streptococci of various types invade the tissues and body fluids long before the colon bacillus, and are, moreover, almost always present where the latter is found. A long series of blood cultures taken by workers in our laboratories from the arm vein immediately or shortly after death, as well as numerous cases reported in the literature, serve to demonstrate this fact. Numerous investigators have further shown that this invasion by streptococci is more commonly antemortem and often occurs as the so-called agonal infection.

[7] Palmer and Henderson, loc. cit.

[1] Read before the American Association of Pathologists and Bacteriologists, Washington, May 10, 1916.

From these cases illustrating the invasive power of the streptococci under definite recognizable conditions of damaged resistance we are able to follow a graded series of cases in which invasion took place hours, weeks, months, and years before death as also innumerable examples when death did not result from the invasion. Many investigators believe that streptococci are frequently invading the body, but that under conditions of relatively good health they are being continually destroyed.

It is certainly true that streptococci invade the blood stream more often than most other bacteria. Their demonstration is not always easy, as they frequently only temporarily invade the blood. It is not uncommon to find that 10 c.c. of blood fails to reveal the organisms while 15 c.c., 20 c.c., or 25 c.c. may be required to demonstrate a single colony. We are limited, for obvious reasons, in the amount of blood we can take, and therefore we endeavor to choose a time when the number of bacteria in the blood is greatest. There is no royal road to successful blood cultures in many of these cases. Serum broth with or without carbohydrates is probably the best medium and by adding a tube of melted agar, anaërobic cultures are readily made. In this as in many similar tests a positive result is important; a negative leaves the question open. There is ample evidence to show that streptococci found in various lesions of the body have probably been distributed by the blood stream, but the invasion from the nearest naturally infected parts of the body must always be first considered.

The portals of entry for streptococci are wide-spread and do not play as important a role in the invasion as is the case with other bacterial groups. The organisms may enter the body from the mucous membranes of the throat, that of the intestinal tract, the uterus, from the skin, and many other points. Naturally, the conditions will vary somewhat according to the types of tissue encountered by the organisms. Whether they further increase in numbers and bring about damage depends largely upon the relative susceptibility or resistance of the different tissues of the body; that is, the environmental conditions they encounter. I do not assume there is a specificity on the part of the streptococci as to what tissue or organ they attack, but, granted that the natural distribution plays no part, I am convinced that they locate in whatever areas offer the proper conditions of relative susceptibility. No two animals offer the same conditions for the invasion of bacteria nor identical susceptibility or resistance in all their tissues. It is true, no doubt, that a group of animals or human beings living under the same conditions will tend, more or less, to similar tissue susceptibilities, and that at different seasons of the year alterations in temperature and moisture of the air, changes in food and ventilation, and number of other environmental conditions will tend to alter these susceptibilities in the entire group.

Nevertheless, certain individual differences will still persist. Many experiments on animals demonstrate this variability in tissue susceptibility in different groups of the same race of animals. Everyone is familiar with family susceptibility as well as individual variations following the same infection. These facts are often forgotten when animals are used in the study of bacteria, but being remembered will often prevent misinterpretation of results.

By virulence of the streptococci I mean something further than invasive power. Virulence is the ability of bacteria to multiply in the tissues, to resist the defensive mechanism, to increase the susceptibility (probably by toxins) of the tissues, and to prepare the way for the manifestations of pathogenicity. If the virulence is high the incubation period is reduced and the pathogenic characters are seen early. It is relatively common in infections with hemolytic streptococci to have a slight local reaction at the portal of entry. The virulence in these cases is very intense and the resistance is rapidly overcome.

Three groups of streptococci have been arranged as follows: (1) Those lacking in invasive, virulent, and pathogenic qualities; these include the strictly saprophytic forms, which I believe are very rare. (2) Those with well-developed, slowly acting virulence (possibly on account of a similarity of metabolic activity to that of the host) but with definite and eventually, when the infection continues, severe pathogenic powers; in this group we have the Streptococcus viridans organisms. (3) Those with powerful invasive power, active virulence setting up violent defensive reactions and exhibiting a high pathogenicity. Under these we have the hemolytic streptococci.

There are a number of conditions that modify the demonstration of these qualities. The portal of entry may be more or less favorable to a rapid manifestation of all these characters. Locally, highly resistant tissues may check either the invasion, the further growth of the bacteria (virulence), or the pathogenicity, while other tissues offer more favorable conditions, particularly mucous membranes in which disease processes, set up by the invading organisms or other bacteria, may offer a ready entrance for the bacteria to underlying structures or the general circulation. The number of bacteria invading the body will also greatly influence the virulence and the pathogenicity. This is particularly to be remembered in consideration of invasion from primary infected foci such as are found in the tonsils, gums, intestinal tract, uterus, and other parts. These local foci also serve as points in which the bacteria may fully develop their invasive, virulent, and pathogenic characters. They serve, as it were, as training grounds for the bacteria. The increase in these qualities is within fairly narrow limits. The hemolytic streptococci, which are the strains capable of becoming highly virulent and pathogenic, may here not only increase in

numbers but develop more rapidly these qualities. The members of the Streptococcus viridans group may also have the opportunity in these foci of increasing in their characters, but only within the limits of the group, and at no time do they develop the type of virulence and pathogenicity found in the streptococcus hemolyticus group.

There is another condition found in these foci which has led to much confusion among early investigators, and that is the presence in them of a mixture of bacteria. Such foci develop as the result of a lowering of resistance in the local tissues and the invasion of bacteria of the grade of virulence proportionate to the condition. Following this several things may happen: the bacteria may increase in disease-producing power within their capabilities or they may prepare the way for more vigorous types of organisms, the two or more growing commensally or until the weaker succumbs. At any time during this process a further invasion of tissue or the blood stream may occur by the original organisms, the mixture, the dominant organisms in the mixture, or by the surviving strains. In any case the organisms invading the body will either be overcome or will cause secondary foci in those tissues in which the environment resulting from the noxious influence of manifold agencies including toxins is favorable for their development.

These possibilities which I have cited are what actually occur. We find infected foci with one type of streptococcus or with two or several types as well as with other bacteria. We can frequently demonstrate the entrance of a new type and its survival in various stages of the process. When the blood stream is invaded it is most commonly by one organism, but by no means infrequently by two. This blood stream invasion is mostly transitory, but sufficient to give rise to secondary foci from which corresponding types of organisms may be recovered. Furthermore, these secondary foci may serve as new distributing points. Wrong interpretations of these findings have led to most astonishing "biological alterations and mutations."

What appears to be the obvious focus of infection is not always the source from which invasion actually occurs. An inflammatory process of the intestinal tract synchronous with pyorrhea, for example, may be the condition leading to the invasion of bacteria. It is, indeed, often extremely difficult to be certain of the conditions present, and we should be very careful in drawing dogmatic conclusions from our necessarily limited findings.

There are certain states of lowered resistance that appear to be favorable for the invasion and activity of one or other of the two main streptococcus groups. In the puerperal state and in scarlet fever the conditions usually favor an infection by the hemolytic streptococci while chronic irritations, such as are found in the stomach, kidneys, and other organs from a variety of causes,

general lack of tone following sedentary life, exposure to cold and dampness, and many other similar, often temporary, lowerings of resistance offer conditions most suited to the attack of the non-hemolytic streptococci. In perforations of the intestinal tract in which the non-hemolytic strains are numerically greatly in excess of the hemolytic, judging from cultures of the intestinal contents, it is usually the latter which survive and cause the severe results, which means that the hemolytic forms can withstand the active defenses of the body better than the non-hemolytic; in other words, they are more virulent.

The members of the hemolytic streptococcus group include the strains with the highest virulence and pathogenicity. They are the causative agents in the most severe types of streptococcal disease, such as severe septicemia, erysipelas, peritonitis, and other pyogenic infections. These infections give severe local or general reactions and are often fatal, but even with recovery we have the clinical picture of severe acute disease.

The streptococci of the viridans group, on the other hand, are the common cause of chronic infections. They have high invasive power and attack tissues in a state of lowered resistance, stimulate little reaction on the part of the body, apparently render the tissues more susceptible to reinfections, and death, if it occurs, only follows after a prolonged course or repeated reinfections. Clinically these cases are characterized by a relatively mild and chronic course with frequent exacerbations. Occasionally a Streptococcus viridans strain prepares the way for a hemolytic strain and the disease becomes a more severe one, and in cases recovering from a hemolytic streptococcus infection an invasion may occur with one of the non-hemolytic forms.

A proper classification is necessary to enable us to recognize the various varieties of streptococci. The method which I have been following for some time and which is published this year has enabled me to greatly enlarge my views on the invasive and other qualities of the streptococci. I have been able to recognize mixtures of different streptococci belonging to both of the two main groups and to trace the source of the invasion in many cases. There is one important point which has been noted in this study, and that is that the streptococci are not specific in their disease production. There is no evidence to support the view that only one type of streptococcus produces endocarditis or nephritis or gives rise to septicemia in the puerperium, scarlet fever, or other conditions of lower resistance. Neither do I believe that one streptococcus is responsible for all the ill effects in all of these cases. Streptococci of several kinds live in symbiosis in the mouth and the intestinal tract. They are often found in mixtures in other infected areas as in the peritoneal, pleural, and other cavities. The blood stream may be invaded by more than one type, although, as a rule, we only

recover one. It is, therefore, not surprising to find different organisms locating in various damaged areas. Under these conditions by the use of the hemolytic test alone we are liable to draw erroneous conclusions. Thus by this single method, without the carbohydrate fermentation tests, the various members of the viridans or hemolytic groups cannot be distinguished.

There are many interesting points for discussion in tracing the source of many of the streptococci. The streptococcic flora of the mouth has always been confusing. The finding of mouth streptococci in the air of rooms as shown by Gordon may be taken as indicating pollution of the air from the oral cavity and thus the flora of the mouth is continually being replenished from the mouths of others. Another source of origin for these streptococci appears to be cows' milk which in turn is subject to contamination from the cows' feces while still a third source is the air streptococcus derived from horse manure. In the mouth cavity many of these strains find favorable conditions for further development. Broadhurst has shown that many streptococci, being swallowed in the sputum, can pass through the stomach without being destroyed in the limited time by the gastric juices. In the intestinal tract the cultural conditions are markedly different from those of the mouth, and many of these strains are destroyed, while others, especially the more vigorous forms, such as Streptococcus fecalis and Streptococcus equinus, flourish and produce a flora quite different from that found in the mouth.

It cannot be too often repeated, however, that the entire flora of any region of the body may be suddenly changed by alterations in the food supplied to the bacteria, the reactions of the secretions, the presence of inflammation, and many other important environmental changes. Particular streptococci finding these new conditions favorable, multiply rapidly and the former inhabitants are crowded out. In diphtheria, for example, streptococci may greatly increase in numbers and seriously complicate the conditions, as has been repeatedly pointed out by Le Gros and others. Although the streptococci present in the greatest numbers in normal saliva and intestines are of the viridans group, a careful search will almost always reveal members of the hemolytic group, and these, as experience teaches, are the strains most capable of producing severe infections. In this connection the influx of strains from disease sources outside of the body, in which the streptococci have developed to a high degree, their disease-producing characters must not be forgotten.

It is beside the point to argue that streptococcus infection in rheumatism and other diseases is a secondary invasion. It is most certainly true that in practically all our infections the bacterial attack is secondary to the necessary conditions of lowered resistance. In many of these arguments one is reminded of Pettenkofer's

demonstration to prove that the cholera vibrio does not always cause epidemics of cholera.

The condition of lowered resistance in the Streptococcus viridans infections are receiving much attention but we are only on the threshold of this study. When the streptococci have established themselves within the system we are usually at a relatively late stage of the disease. Libman has shown that in viridans endocarditis the cases may become spontaneously bacteria-free. The work of many of the German workers would indicate, though on somewhat dubious grounds, that the viridans endocarditis is almost always eventually fatal. There is no doubt that with more careful blood cultures the frequency of viridans infection in the earliest stages is being shown and the recurrent attacks are being guarded against (Oille, Graham, and Detweiler).

Spontaneous streptococcus infections in animals is a frequent occurrence. I have isolated streptococci from about half of 200 guinea-pigs infected spontaneously. In most of these the streptococcus infection was the cause of death, but in others the streptococci were definitely secondary invaders during the course of other infections. In certain animals dying of a hemolytic streptococcus infection of the lungs, for example, non-hemolytic streptococci have been isolated from the peritoneal fluid. I have further demonstrated that streptococci found in the alimentary tract will invade the animal body following injections of dead or living colon bacilli as also after injecting various forms of streptococci. Numerous similar results have been recorded in the literature, but not uncommonly these have been misinterpreted.

It must not be forgotten that in injecting streptococci into animals we are overlooking some of the most important characters of these bacteria. Subcutaneous and intraperitoneal injections of large doses may serve as tests for the further invasive power of the bacteria from these sites, modified by the local injury resulting from the injections, while intravenous injection completely ignores the invasive character. The streptococci by this latter method, finding themselves in the circulation, naturally locate in various organs, and, according to the grade of virulence, will multiply in those tissues in which the susceptibility is of the corresponding grade. The irritation, both mechanical and that arising from the products of growth in the vehicle, will frequently bring about local reactions, which may or may not favor the development of virulence. Infiltration of the tissues with polymorphonuclear leukocytes will frequently follow large injections while only mononuclear response may result from small doses.

Streptococci derived from sources in which the natural infection did not result in a polymorphonuclear reaction may give rise, when injected in large doses, to such a reaction. It is therefore not to be concluded from the unnatural conditions of such experi-

ments that the response elicited is fundamentally characteristic of the bacteria. The study of natural infection demonstrates that the two main groups of streptococci call forth quite different responses, and animal experiments would be of value if we could determine the minimal dose which calls forth any reaction, as this would more nearly approach the natural condition. The products of growth of the bacteria, be they toxins or other excretions, probably determine the character of the response in susceptible tissues, and these two groups differ in the type of reaction they stimulate, the hemolytic streptococci calling forth more active responses and the non-hemolytic a slower and more chronic type of reaction. If we use the same dose of one streptococcus with a certain virulence and find the same tissues affected in the majority of the injected animals it will serve as a test to indicate the susceptibility of these tissues in the particular group of animals. Even varying doses may at times demonstrate the same thing. Further, this same streptococcus having had its virulence raised will attack other tissues which were resistant in the previous experiments. All these and many other points serve to emphasize the importance of the relations existing between the host and the infecting organism.

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REVIEWS

SYPHILIS. By LOYD THOMPSON, M.D., Physician to the Spyhilis Clinic, Government Free Bath House, Hot Springs, Arkansas. Octavo, 415 pages with 77 engravings and 7 colored plates. Philadelphia and New York: Lea & Febiger, 1916.

OBVIOUSLY in the preparation of this work, it has been the intention of the author to present the subject of syphilis as concisely as practicable. Historical and theoretical matters have been given only the consideration commensurate with the practical nature of the book, which although small, is unusually well condensed and one of the best that has thus far appeared. The contents are well divided into three parts: The first comprises a consideration of syphilis in general, with reference particularly to the acquired form; the second is devoted to the various systemic tracts, glands, skeleton, musculature and special organs; the third treats of congenital and regional syphilis.

The author fully appreciates the epoch-making strides that have marked the progress of our knowledge of this disease during the past decade, and accordingly devotes a considerable portion of the work to diagnosis and treatment. The chapter on laboratory diagnosis is especially commendable, although we would censure the author's reliance upon cholesterinized antigen in the performance of the Wassermann reaction.

Thompson appreciates the fact that syphilis is fundamentally a genito-urinary disease, but wisely states that it is a disease requiring knowledge in all fields of medical practice. The author acknowledges his indebtedness to the extensive literature on syphilis, although he has added his own personal views and experiences, as attested by numerous new illustrations in the test. B. A. T.

AMERICAN PUBLIC HEALTH PROTECTION. By HENRY BIXBY HEMENWAY, A.M., M.D. Pp. 283. Indianapolis: The Bobbs-Merrill Company, 1916.

THIS book, in "novel" form, is dedicated to the women of America and is a popular appeal to them, as "the power behind the throne," to use their influence for the advancement of public health. They

are warned that they themselves as amateur sanitarians should not attempt to determine administrative policies or legislative provisions, but are told that their duty above all else lies in encouraging the appointment of competent full-time health officers. It is especially emphasized that practising physicians, both because of their inadequate public-health training and also because of the enmity which is likely to arise between a good health officer and practitioners, should not be health administrators.

Among the other subjects dealt with are the development of public health in the United States, the national health agencies, the changed social and economic conditions due to the advancement in the science of public health, the medical inspection of schools, and the organization of health departments. All these matters are discussed in a popular vein, and yet a great deal is said that is as unrecognized by physicians as it is by the laity. Such books will certainly aid materially in the bringing about of a larger vision of the problem of public health. T. G. M.

THE CATARRHAL AND SUPPURATIVE DISEASES OF THE ACCESSORY SINUSES OF THE NOSE. By ROSS HALL SKILLERN, M.D., Professor of Laryngology, Medico-Chirurgical College; Laryngologist to Rush Hospital, Philadelphia. Second edition. Pp. 418; 287 illustrations. Philadelphia and London: J. B. Lippincott Company, 1916.

MANY changes have been made to the text of the first edition of this excellent work, though, as a rule, these changes consist of adding details and methods heretofore not gone into so elaborately.

Among the newer subjects are Canfield's operation on the maxillary sinus compared with the preturbinal method; also Halle's new frontal sinus operation, with description and illustrations of this method, together with a complete revision of the chapter on the sphenoid sinus.

It is gratifying to note that the author has modified to a great extent some of his ultraradical ideas by giving considerable attention to the phase of treatment which deals with the judgment of the attending surgeon as to whether or not to choose an operative procedure.

The after-treatment of sinus operations is gone into more thoroughly than formerly, and possibly could be dwelt upon even to a greater extent. The end results of sinus operations could also be brought out to better advantage in spite of the addition of a compilation of the American mortalities following the Killian operation.

The work, as a whole, meets the demand for a clear and concise treatise on nasal sinuses and their operations. The author not only writes from his own personal view-point, but also has, whenever possible, mentioned other methods, with copious references to the literature on the subject.

There is possibly no work in the English language that better meets the aim of this book, namely, that of presenting an exclusive treatment of the nasal sinuses, meeting the demand both of a text-book and one of reference. B. D. C.

Sexual Impotence. By Victor G. Vecki, M.D., Consulting Genito-urinary Surgeon to the Mt. Zion Hospital, San Francisco. Fifth edition. Pp. 405. Philadelphia and London: W. B. Saunders Company.

Since 1888, when the first edition of this book was published, the development of the science of euology has made possible more accurate diagnosis and consequently a better therapy for sexual impotence. The author has revised and modified the work for this edition chiefly from the stand-point of treatment, but his ethical and sociological views remain unchanged, though they differ in many respects from those generally held by the profession. The well-written chapters on anatomy and physiology are followed by an elaborate description of the forms of impotence. The chapters on diagnosis and prognosis are disappointingly brief.

In the chapter on treatment the author discusses all the usual and nearly all the unusual drugs and therapeutic methods. He says: "The great number of methods and remedies speaks for the small value of most of them, and yet there is hardly any one of them that could be entirely dispensed with." The excellent table of contents and index are useful in correlating the text, which has a tendency to be vague in its application. The printing and binding are up to the usual excellent standard of the publishers.

G. M. L.

What to Eat and Why. By G. Carroll Smith, M.D., Boston, Mass. Second edition, thoroughly revised. Pp. 377. Philadelphia and London: W. B. Saunders Company.

This book is primarily intended for physicians, but is written in a semipopular style. Under the caption of various diseases it considers foods and diets which, in the opinion of the author, are suitable to these respective conditions. There is contained a good

deal of useful information together with rather individual generalizations which are of less value. Certain important phases of treatment are omitted, as, for example the "starvation" treatment of diabetes, and there are included such sections as that on "diet in uric-acid diathesis." The language is rather loose in structure, and in some places ungrammatical. R. P.

Der Starrkrampf, seine Entstehung und Behandlung. von Prof. Dr. Ferdinand Blumenthal, Leitender-Aerzt der inneren Abteilung des städt. Krankenhauses Berlin-Lichtenberg. S. 79. Wien: Verlag von Urban & Schwarzenberg.

This brochure is extracted from Blumenthal's article upon tetanus, which appeared the previous year in Eulenburg's *Real-Enzyklopädie*. It was published separately by the author at the request of numerous physicians who found themselves suddenly confronted with tetanus in the European War when, as a matter of fact, they had seldom or never seen a case of the malady previously.

The brochure opens with a description of the incidence and natural history of tetanus, and then discusses human tetanus, experimental tetanus, disposition and natural immunity, methods of conferring immunity, metabolic changes, serum treatment, prophylactic treatment with antitoxin, serum preparations, serum anaphylaxis, other methods of treatment, symptomatic treatment of the convulsions, and the feeding of tetanus patients.

The brochure is written by an authority on tetanus, and its perusal shows that the disease is a very interesting one to study. The author presents the most modern and accepted form of treatment, which is quite the same as that used in our own great metropolitan hospitals. The monograph is timely and useful.

P. G. S., Jr.

Cerebellar Abscess: Its Etiology, Pathology, Diagnosis, and Treatment, Including Anatomy and Physiology of the Cerebellum. By Drs. Isidore Friesner and Alfred Braun. Pp. 186. New York: Paul B. Hoeber Company, 1916.

The authors begin with the anatomy of the cerebellum, in which many diagrams are used to illustrate the connections of the cerebellum with the cerebrospinal system.

The next chapter concerns itself with the physiology of the cerebellum, in which the various opinions of those who have worked in this field are presented, there being a short summary of Barany's

investigations and his tests. Then follows the etiology and pathology of cerebellar abscesses. This undoubtedly is the best part of the book, and gives the experience of the authors in this field. In the next chapter advantage is taken of the recent literature, and the symptomatology of the cerebellum is presented perhaps better than is the case with most text-books. In common with most articles on cerebellar symptomatology, however, they still cling to the idea that a cerebellar lesion should give a certain group of symptoms, such as hypermetry, asynergia, tremor, disturbances of tone, etc., when, as a matter of fact, they all depend upon the one primary disturbance of function due to a lesion of the cerebellum, that is, asynergy. This, however, is a minor error, for the important thing is that all the symptoms are given, and anyone reading this chapter would undoubtedly attain an adequate idea of cerebellar symptomatology. The illustrations of the pointing tests are not adequate. The last chapter concerns itself with prognosis and treatment. The authors rightfully assume that early surgical measures should be employed. They give an adequate review of the literature and their own experiences.

On the whole, this book represents a very good attempt to present the subject of cerebellar abscess, and is adequate when it is considered that it will be read mostly by others than neurologists. It is always rather risky for a specialist to write upon a subject which is not particularly in his field. If, for example, a neurologist should essay to write about a nose, throat, and ear condition he would naturally fall into many errors, for he could hardly be expected to know the subject as well as those who limit their work to these subjects. The reviewer, however, has no doubt that in subsequent deserved editions of this work such errors will be eliminated. T. H. W.

Syphilis and the Nervous System. By Dr. Max Nonne. Authorized translation from the second revised and enlarged German edition. By Charles R. Ball, M.D. Pp. 450; 98 illustrations. Philadelphia and London: J. B. Lippincott Company, 1916.

The second edition of Nonne's book is a vast improvement over the first, the review of which was published in this Journal some years ago. Practically no changes have been made in the presentation of the organic matter, for the symptoms of involvement of the nervous system are the same now as they always have been.

When the first edition was written the Spirochete pallida, the application of the Wassermann and other serum tests, to which the author has contributed largely, and the use of salvarsan were just becoming known. Therefore, there is scarcely any mention

of these matters in the first edition. In this work the serum tests, especially Nonne's own tests, are elucidated and their value shown. It is hardly necessary to comment on this subject, for it is well known to the profession and Nonne does not present anything that is new. His views, however, upon the use of salvarsan in syphilis of the nervous system are very important. He is of the opinion that salvarsan in individual cases gives a quicker and a more far-reaching result than may be obtained with the use of mercury and iodide, but he says that in by far the greater number of cases the superiority of salvarsan over mercury and iodide is not apparent. In cases of gummatous disease of the central nervous system immediate salvarsan treatment may be said to be especially indicated. In specific disease, in which the vital centers are involved, it is especially contra-indicated. He does not think it is of more value than mercury in tabes nor of more value than mercury or iodide in paresis. He does not see any special advantage in the Swift-Ellis serum treatment. He advises the combined use of salvarsan and mercury. He quotes a number of instances in which cases of undoubted paresis have been cured. Some of these he had under his observation for over twenty years. To anyone interested in syphilis of the nervous system this excellent translation of Nonne's book gives by far the most adequate presentation of the subject.

T. H. W.

Annual Report of the Department of Pathology of the Johns Hopkins University and Hospital I. The Johns Hopkins Reports, Vol. XVIII, Fasciculus I. Pp. 102. Photographs, drawings, charts, and tables. Baltimore: Johns Hopkins Press, 1916.

The volume is the first issue of the annual report of the department of pathology and embraces abstracts of the articles which have already appeared and short outlines of work which had not yet been published in scientific periodicals at the time the volume was printed. A brief review of the original articles given in full and those abstracts in which there is no promise of further report is here given.

Goodpasture and Clark describe the isolation of a toxic, thermostabile element associated with beta-nucleoproteid in pancreatic tissue. This substance is probably proteid, as it gradually autolyzes to destruction, is not due to the action of trypsin, and is toxic for animals.

Schmeisser and Winternitz present data going to show that the acute and subacute diseases of the fowl, fowl typhoid, and leukemia are due to Moore's Bacteria sanguinarium, and are in all probability phases of the same infection.

Winternitz's work supports the theory that the islands of Langerhans may be qualitatively or quantitatively altered in diabetes, that their significance is not understood, and that the pancreas is but "one link in the chain that controls carbohydrate metabolism."

The same author reports a case of generalized miliary tuberculosis resulting from an extension of a tubercular pericarditis into the right auricle. (Without desiring to be captious the reviewer thinks it is better to use the adjective "tuberculous" for a lesion due to the bacillus of Koch.)

An interesting case of acute hyphophysitis arising by extension, reported by Boggs and Winternitz, showed no hyperglycemia, glycosuria, or localizing signs.

More interesting case histories close the scientific reports in the volume.

The last few pages are devoted to a description of the workings of the department of pathology. The 5000 autopsy records collected in seventeen years are to be combined in a single volume, ready in 1917, according to a plan worked out by a statistician of a large insurance company coöperating with the pathologists. Sample charts and filing cards are depicted. The classifications are only in gross organ systems, and the diagnosis will have to be inserted in symbols. It is not quite clear how the record book and filing cards are to be completed. The latter seem too comprehensive for a mere index and too small for a protocol. Autopsy records for the past five years arranged according to service and percentage show a distinct increase in number. The pathological and clinical staffs have conferences each week upon autopsies performed. Further coöperation is indicated by an attempt to have junior members of the clinical staff working in the laboratory.

The book is a distinct stimulus to community of interest between those at the bedside and those at the autopsy table. The reports are especially commendable in their brevity. H. F.

American Year-Book of Anesthesia and Analgesia. By F. H. McMechin, A.M., M.D. (Editor). Pp. 415; illustrated. New York: Surgery Publishing Company, 1916.

The editor states that this year-book was established for the collation of the world's ultrascientific researches for the practice of anesthesia and analgesia and that the contributors have scoured the world's literature to make the context as comprehensive and exhaustive as possible. Thirty-one papers are presented by representative writers, and while original research has been given a prominent place the clinical aspects have by no means been neglected. Besides a general survey of the progress being made in these subjects,

there are provided those special advances having a direct bearing on the individual requirements of the practising surgeon, dentist, anesthetist, etc. The thirty-one papers cover pretty much the whole field of anesthesia and analgesia. The following are a few of the clinical subjects discussed: Chloroform poisoning; use of music in anesthesia; effect on kidney function of anesthesia; manufacture of nitrous oxide for hospitals; ether-colonic anesthesia; nitrous oxide in obstetrics; somnoform in dental operations; local anesthesia in connection with after-pain for ano-rectal surgery, for hernia operations, and for prostatectomy. There is one paper on injecting the Gasserian ganglion and two on spinal anesthesia. When one wishes to use any of these forms of anesthesia this work must be of great service in furnishing full information in each instance. T. T. T.

THE PRACTICE OF OBSTETRICS. By J. CLIFTON EDGAR, Professor of Obstetrics and Clinical Midwifery in the Cornell University Medical College; Visiting Obstetrician to Bellevue Hospital, New York City; Surgeon to the Manhattan Maternity and Dispensary; Consulting Obstetrician to the New York Maternity and Jewish Maternity Hospitals. Fifth edition, revised. Pp. 1024; 1316 illustrations. Philadelphia: P. Blakiston's Son & Co., 1916.

THE present volume follows closely the lines of the previous editions, and for this reason an extended comment seems unnecessary. The revision, if it can be so termed, consists in the addition of a few pages on painless labor and twilight sleep, pituitary extract in uterine inertia, and the artificial feeding of infants.

The introduction of pituitary extract must rank as one of the important recent advances in obstetrics. However, the usefulness of the drug is counterbalanced with possible dangers to the mother and child from its use. The author reviews the indications for its administration, cautioning against the uncertainty of its action in some cases. Among the contra-indications omitted is that of using this drug in cases with high arterial tension, as in toxemia of pregnancy. Anyone who has had a considerable experience with pituitary extract in labor will agree with the author that "it should not be employed for inertia in any stage of labor unless anesthesia is at hand for immediate use, and preparation complete for immediate operative delivery, if necessary."

From a study of a sufficiently large number of parturients treated with morphin and scopolamin in an effort to secure the so-called twilight sleep, the author concludes that the method is not entirely free from danger to the two parties concerned. He has found labor prolonged, operative interference more frequently demanded, with a

higher percentage of maternal traumatism, and an increased degree of cyanosis and asphyxia in the infant, with an occasional stillbirth from the use of morphin and scopolamin. He draws more favorable conclusions regarding the use of nitrous oxide and oxygen analgesia in labor.

The chapter on artificial feeding of infants has been considerably changed and new tables of formulas added. A new type of lung-motor for the treatment of asphyxia and a new type of incubator for premature children are pictured.

The book will undoubtedly continue to be regarded as a standard authority on obstetrics. P. F. W.

THE DREAM PROBLEM. By DR. A. E. MAEDER, of Zürich. Nervous and Mental Disease Monograph Series, No. 22. Pp. 43. New York: Nervous and Mental Disease Publishing Company, 1916.

THIS is No. 22 of the monograph series issued by the *Journal of Nervous and Mental Disease*. This small essay of 43 pages is a paper read at the Congress of the Psycho-analytical Society at Munich, September, 1913, published in the *Jahrbuch f. Psychoanalyse und psychoanalytische Forschungen*, 1914. The paper concerns itself with the certain phases of the dream problem. A difference of opinion has arisen as to the interpretation of dreams between Freud and the so-called Zürich school led by Jung. The author, while giving credit to Freud that neurotic symptoms must be regarded as unsuccessful attempts at cure, seeks to establish that the axiom of the dream as a wish-fulfilment is too indefinite, for it fails to embrace the important teleological side of the unconscious function. Maeder regards the dream as the means of expression of the unconscious, and tries to show there is a constructive phase, and that one should regard the dream not only as a problem of wish-fulfilment but also as an effort at cure. He gives an interesting analysis of a patient and compares his interpretation with that of Freud. To psychoanalysts this paper is, of course, very interesting. To those not believing in psychoanalysis the paper is, nevertheless, interesting reading. T. H. W.

INSTINCT AND INTELLIGENCE. N. C. MACNAMARA. Pp. 216. London: Henry Frowde, Oxford University Press. Hodder & Stoughton, Warwick Square, E. C.

PERHAPS the best idea of this book is expressed in the author's preface: "The meaning of the term education is 'to draw out what is in a child;' it therefore includes the training of his inherited instinc-

tive disposition or character as well as the 'putting in' needful knowledge or the 'instruction' of his intellectual faculties. Educationists of the present time appear to exaggerate the importance of training the intellect, and are apt to overlook the fact that each individual possesses certain instinctive qualities which to a large extent determine his behavior throughout life. These qualities, which no human power can eradicate, may, however, be favorably modified by appropriate training. In the following pages we have endeavored to give an outline of the evidence, and the reasons upon which we rely to prove that the instinctive behavior of human beings depends on work performed by definite parts of the brain; consequently, education has not only to deal with the training of something immaterial which we call mind or consciousness, but has, first and foremost to deal with the proper development of the nervous substance of that part of the brain the orderly working of which is essential for the occurrence of instinctive, and intellectual phenomena."

The author then begins with the anatomy and physiology of the ameba and then goes on from this to the higher animal until he finally arrives at the nervous structure of the human being. He advocates the free play of children's actions and is an advocate of the Montesson system.

The book necessarily is very sketchy, but gives an adequate idea to those who wish to have a clearer knowledge of the nervous anatomy, which is the basis of all instinct and intelligence.

T. H. W.

Hand-book of Massage for Beginners. By L. L. Despard, Member and Examiner, Incorporated Society of Trained Masseuses. Pp. 247; 88 illustrations. London: Henry Frowde and Hodder & Stoughton.

This is an admirable book in which the subject is very simply treated. Mention is made in the introduction of carrying on the work under the direction of a physician, and appropriate stress is laid upon the limitations of this form of treatment.

Chapter I treats of the manner in which massage and exercise affect the body's tissues and fluids.

Chapters II, III and IV describe the various movements (active and passive) necessary in applying general and special treatment.

Chapters V to XII deal with the treatment of diseases and deformities in which manual methods have been proven useful.

A useful chapter on Bandaging and a short one on War Injuries are followed by the last chapter, which treats of Medical Electricity.

E. C. L.

THE BOOK OF THE FLY. By G. HURLSTONE HARDY. Pp. 124; 6 figures and 7 plates. New York: Rebman Company, 1916.

AT this time when the method of disease dissemination is a matter of such vital importance this book on the fly question becomes of especial interest and value. The major portion of the volume is devoted to the general life history, anatomy and diverse habits of the various varieties of flies. This of necessity makes much of the book somewhat tedious for the lay reader, with its scientific terms, and to the naturalist it presents nothing new. The chapters dealing with methods for the extermination and control of the fly nuisance are attractive and of considerable value. The whole book is well written and remains a complete presentation of the fly problem. As such it must take its place in the history of the battle being waged for the extermination of this pest. T. G. S.

A REPORT ON RESEARCHES ON SPRUE IN CEYLON. By P. H. BAHR, M.A., M.D., D.T.M. and H., M.R.C.P., M.R.C.S. Pp. 155; 9 illustrations. London: Cambridge University Press.

WHILE not on a subject of every-day interest to the physician of the temperate zone, this monograph makes interesting reading. It is clear that the author has investigated his subject with great zeal and care, and has applied all the resources of modern medicine to his task. Some of the researches seem to point to the conclusion that an infection with the thrush fungus is the cause of the disease. The book is well arranged, and the illustrations are unusually well produced. A. G. M.

NERVOUS CHILDREN. By BEVERLEY R. TUCKER, M.D. Pp. 510. Boston: The Gorham Press, 1916.

THIS book is just what it claims to be, a bugle call to the army of workers with children to "prevent" instead of "cure." It opens with a very general description of the physiological basis for nervousness and leads on through successive chapters on heredity and environment, sexual hygiene, and the training of nervous children, up to an outline of nervous and mental diseases of childhood. The book gives little definite advice except perhaps in the chapter on "habits." It makes excellent and profitable reading for those who wish to know this subject from the stand-point of discovering (but not especially helping) that ever-present product of our civilization, the nervous child. A. G. M.

THE ALLIGATOR AND ITS ALLIES. By ALBERT M. REESE, Professor of Zoölogy in West Virginia University. Pp. xi, 342; 52 figures; 28 plates. New York: G. P. Putnam's Sons.

ALTHOUGH regarded by the publishers as a book of general appeal, this treatise will doubtless find a large acceptance only in the hands of specialists in herpetology and embryology. The only part which might concern others is the first chapter on the biology of the crocodile. While in part a compilation of information regarding this group of reptiles, there is much of original information coming from the author's somewhat extensive experience with the American forms. This is particularly true of the chapter on the development of the alligator, which occupies one-third of the book, and is a reprint, in part, of an earlier paper. The illustrations, many of them original, are good and the typography is excellent.

McC.

CEREBROSPINAL FEVER. By THOMAS J. HORDER, M.D., Assistant Physician to St. Bartholomew's Hospital. Pp. 179; illustrations 17. London: Oxford University Press.

THIS small book is essentially a monograph on the subject of cerebrospinal fever. It is called forth by the present prevalence of the disease in England, and among English troops. There is interesting history which notes the various epidemics occurring since 1805, when cerebrospinal fever was first recognized as an entity. Especial mention should be made of the chapters on modes of infection and prophylaxis. Indeed, the treatise is quite complete, and all that is definitely known of cerebrospinal fever is to be found clearly stated in an easily accessible form.

A. G. M.

MEDICAL HINTS. By COLONEL J. EDWARD SQUIRE, M.D., F.R.C.P., D.P.H. 128 pages. London: Oxford University Press.

IN reading this book one cannot but be impressed with its value for those for whom it was written—namely, the medical officers of an army. It is refreshing at a time when so much surgical is to be read of war to find this little volume devoted to things medical. The more common medical conditions to be met with in war time are concisely dealt with. There are excellent chapters on parasites and poisons, including bichloride, alcohol, and tobacco, and the remarks about malingering and marching are especially noteworthy.

A. G. M.

THE ADOLESCENT. By J. W. SLAUGHTER. Pp. 100. New York: The Macmillan Company.

ANYONE who is searching for a study of the psychology of the adolescent will read this book with much pleasure and profit. The explanation of mental processes, desires, actions and motives is usually clear, and reflects a vast knowledge of youth. The unfolding of the mind and emotions in an individual is compared to the evolution of the race as a whole. By clear reasoning it seems proved that civilization and a prolongation of adolescence are found together.

Valuable chapters point out the difference between the education of boys and of girls. Juvenile crime, skepticism, adolescent love, and the normal development of the instincts and emotions are other subjects dwelt on in an interesting manner.

The book is especially recommended to teachers. One cannot but wish that he had had someone with the understanding of the author to conduct him through the "storm and stress" of his own adolescence. A. G. M.

BACK INJURIES AND THEIR SIGNIFICANCE UNDER THE WORKMEN'S COMPENSATION AND OTHER ACTS. By ARCHIBALD MCKENDRICK, F.R.C.S.E., Surgeon in Charge of Surgical Roentgen-ray Department, Royal Infirmary, Edinburgh. New York: William Wood & Co., 1916.

THIS book consists of 173 pages and 14 illustrations. The medico-legal aspect of back injuries is emphasized in the preface and also in the context. The first 34 pages treat anatomy in detail. A few pages are devoted to stress and contusions of muscles, also to the healing process. A small portion is devoted to surface anatomy. The mode of examination of the patient and the significance of the history and subjective and objective symptoms have received more or less of careful attention.

The heading Examination is interspersed with anatomical, pathological, and physiological facts. The significance of the Roentgen ray is moderately emphasized.

A considerable portion of the book is devoted to dynamics, under which heading external and intrinsic stress, as applied to this part of the anatomy, and its effect upon the structures, is more or less carefully figured out.

The book to a rather considerable extent is elementary, especially in its dealing with anatomical facts. It is somewhat desultory and poorly arranged. In many places it is unconvincing; however, it is a collection of very useful facts, which should be of decided value to the person interested in back injuries. W. J. M.

Practical Prescribing and Treatment in the Diseases of Infants and Children. By D. M. Macdonald, M.D., F.R.C.P.E. Pp. 193. London: Oxford University Press.

In this little book the author attempts to point out some differences between dosage of drugs in children and adults, and to give brief outlines of treatment in certain of the more common diseases and conditions of childhood. In the first chapter is a plea for carefulness in prescribing and avoidance of certain incompatibilities. There is a chapter on infant feeding which is notably brief. The diet tables contain none of the newer preparations, such as casein milk. The chapter on emergencies contain some helpful suggestions, although the section which deals with the treatment of specific diseases is incomplete even for so small a manual.

It would seem that the book is of little value to the specialist, although it might be of some small service to the general practitioner dealing with children. A. G. M.

The After-treatment of Operations. By P. Lockhart-Mummery, F.R.C.S. Eng., B.A., M.B., B.C. Cantab., Senior Surgeon, St. Mark's Hospital for Cancer, Fistula, and other Diseases of the Rectum; The Queen's Hospital for Children, London; Honorary Surgeon to King Edward VIIth's Hospital for Officers; Special Consulting Surgeon to City of London Military Hospital and Fulham Military Hospital; Jacksonian Prizeman and Late Hunterian Professor, Royal College of Surgeons. Fourth edition. Pp. 275; 39 illustrations. London: Ballière, Tindall & Cox. New York: William Wood & Co.

For the general after-treatment of operation cases this manual fills an important place, and from the very comprehensive way in which the subject is presented it should be in the hands of every house surgeon and general practitioner.

In the present edition much new matter has been added, especially a chapter on the treatment of gunshot wounds, and the chapter on surgical shock has been entirely rewritten, being chiefly a summary of Crile and Lower's contributions on this subject.

The book is well edited and the illustrations are attractive and helpful. Throughout the text there are numerous foot-note histories of cases very aptly illustrating the condition under discussion. There are also many references to the literature. J. C. B.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
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Studies on the So-called Transitional Cells.—Evans (*Arch. Int. Med.*, 1916, xviii, 692) in the present study has made the attempt to clear up some of the uncertainty which exists in regard to the large mononuclear white blood cells, concerning the various types of which, their origin and significance a great deal of confusion exists. In this group the so-called transitional cells stand out from all the rest by reason of their content in granules of an oxydase ferment, as can readily be demonstrated, by the application of the indophenol-blue reaction. Taking advantage of this fact the author has attempted by means of experimental methods, to determine *first* which of the mononuclear wandering cells of the tissues, if any, are lymphoid and which histogenous; *second*, which of the large mononuclear cells of the blood fall into the same groups; *third*, whether the transitional cells of the peripheral blood can be identified with any other mononuclear cells of the blood or tissues; and *finally*, whether all the mononuclear wandering cells of the body exclusive of the small lymphocytes, are of histogenous origin. He has attempted to solve these points by a number of methods including intravenous vital staining, and intraperitoneal vital staining, using various types of dyes. As a result of his studies Evans gives the following grouping of the mononuclear cells: (1) Cells containing an oxydase ferment and not taking the vital stains. (2) Cells containing no oxydase ferment but specifically stained intra vitam. These cells are the normal constituents of the tissues and are of rare and accidental occurrence in the peripheral blood. (3) Cells containing no oxydase ferment and not taking the vital stain, namely the lymphoid elements in which are included the true lymphocytes and probably most of the non-oxydase large mononuclears of the blood. These observations

would seem to refute the theory of Mallory which assumes that all the adult mononuclears of the blood are of endothelial or histogenous origin and supports the view of Aschoff that there is a distinct histogenous and lymphoid group of cells totally distinct from each other. With specific reference to the transitional cells Evans points out that they constantly present the following features: (1) They possess an oxydase ferment readily demonstrable. (2) They are not specifically stained intra vitam. (3) They take up carmin particles from an unfiltered solution. (4) These cells may be found in the spleen and other blood-forming organs, but are not more abundant in the splenic vein blood than elsewhere and are never seen in the omentum, serous fluid or tissues when any polymorphonuclear cells are present. (5) And finally, the evidence is in favor of the view in accordance with that supported by Naegeli, that these cells belong to the granulocyte series and, together with the other granular polynuclear cells, should be regarded as descendants of the myeloblasts of the bone marrow and splenic pulp.

Autogenous Defibrinated Blood in the Treatment of Bronchial Asthma.—Kahn and Emsheimer (*Arch. Int. Med.*, 1916, xviii, 445) have devised a rather interesting method for the treatment of bronchial asthma consisting of the subcutaneous injection of autogenous defibrinated blood. This blood is withdrawn whenever possible, during an asthmatic attack. The theory upon which they base this mode of treatment may be stated in the following way: asthma is presumably due to a spasm of the smaller bronchi and this spasm in turn is probably the manifestation of an anaphylactic condition. It is presumed that the anaphylactic phenomenon represented by an attack of bronchial asthma is to be explained upon the basis of protein sensitization, though whether the protein gains access to the body by the nasopharynx, gastro-intestinal, or respiratory system is not certain. In any event, it is probably absorbed into the blood, and if so, it should be found there most probably just prior to or during an acute asthmatic attack. If these assumptions are true, then it is quite conceivable that immunization by the repeated parenteral injections of autogenous defibrinated blood should be beneficial to the patient. Applying this theory, the patients have secured, in six successive cases, of bronchial asthma, very favorable results as shown by definite improvement generally and a decrease in the frequency and severity of the bronchial asthma attacks. The patients have been able to do more work and have gained in eight. The procedure is simply the withdrawal of about 20 to 30 c.c. of blood into a sterile flask which contains a number of glass beads. By agitation the blood is defibrinated and it is then immediately injected subcutaneously into the loin of the patient. Aside from a little local discomfort, there have been no untoward effects following the injections.

The Relation of the Pituitary Body to Renal Function.—A great deal of work has been done recently in an attempt to demonstrate a relationship between the pituitary body and the kidneys, especially with regard to the etiology and pathology of diabetes insipidus. In the present article Motzveldt (*Jour. Exp. Med.*, 1917, xxv, 153) brings forward further evidence to support a conclusion previously advanced by him to the effect that the pituitary body exerts its essential action

upon the kidneys in the way of *checking* the flow of urine or in other words, the function of the pituitary body with relation to the kidney is one of an anti-diuretic effect, this action being most marked when diuresis is high. In support of this contention the author has previously shown the beneficial effects which have persisted over a period of two years in a case of diabetes insipidus treated with the posterior lobe of the pituitary body. In the present work a more or less constant artificial polyuria was worked out in rabbits by introducing into their stomachs between 150 to 200 c.c. of water. Curves of excretion were thereafter charted out for various rabbits treated with pituitary extracts of a number of different preparations. In addition to noting the effect of pituitary extract, the effects of other drugs such as chloral, strychnia, morphin, caffein, adrenalin, thyroid and thymus glands were noted all under different conditions of administration and both with and without the intermediate action of the nerve supply to the kidneys. As a result of the study the author again comes to the conclusion that extracts of the posterior lobe of the hypophysis, whether given by mouth, subcutaneously or intravenously, are able to check an induced polyuria. This anti-diuretic effect is apparently independent of the changes in the blood-pressure, intestinal absorption or the action of the vagus nerves. One very interesting feature and of practical therapeutic importance was the beautiful demonstration of the fact that the anti-diuretic action of the pituitary is absent or only slightly present, in checking the so-called salt diuresis produced, in this instance, by the ingestion of 40 c.c. of a 10 per cent. solution of sodium chloride. This fact is a further demonstration of the essential difference between water diuresis and salt diuresis and shows the importance of a salt-poor diet in the rational treatment of diabetes insipidus.

Renal Function in Pernicious Anemia. — It has been previously pointed out that patients with severe anemias may give results to a renal test diet which are similar in every detail to those found in advanced cases of contracted kidney. The point first emphasized by Mosenthal has been further studied by CHRISTIAN (*Arch. Int. Med.* 1916, xviii, 430) in a series of cases of pernicious anemia. The data secured from this study indicates without doubt that in severe anemia renal function as measured by diet tests, is disturbed in much the same way as in cases of advanced chronic interstitial nephritis. This is apparently true no matter whether the anemia is in a young or old person. It would seem most likely that the disturbance of renal function is a direct result of the anemia and is the expression either of a nutritional or of a toxic disturbance in the activity of the renal cells. Evidences in favor of this view are shown by the improvement in renal function which takes place parallel with an improvement in the anemia itself. In view of the fact therefore that an advanced nephritic picture may be entirely simulated by cases of severe anemia, it is absolutely necessary to consider the element of anemia whenever one attempts to draw conclusions from renal test diets applied to patients with nephritis. Christian points out however, the fact that this point, though of great importance, is not going to prove a very complicating factor, since, despite their pallor, the degree of anemia in patients with advanced nephritis is very often slight.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

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The Antiseptic Treatment of Wounds.—FELDMAN and WALTON (*Lancet*, December 23, 1916, p. 1043), from a large military experience, deduced the following as the best antiseptic treatment for wounds: The antiseptic, itself, was prepared by rubbing together in a mortar crystals of pure carbolic acid and camphor in equal parts by weight—a perfectly clean sweet smelling liquid being thus obtained. As is the case when using any other application, it is primarily essential to provide adequate drainage. When seen in a relatively early stage the wound, if deep or punctured, should be opened under general anesthesia so as to eliminate, as far as possible, any pockets in the tissues and all foreign bodies, loose pieces of bone, or necrotic tissue should be removed. When the wound has been freely opened sufficient of the liquid is poured in to reach the whole surface of the tissues. In large wounds as much as one or two fluid ounces may be required, although as a general rule one or more fluid drams are sufficient. Drainage tubes are inserted as required and packed around with gauze soaked in the fluid. On the surface dry gauze is applied. It is only necessary to change the dressings every forty-eight hours, when a few drops of the fluid are dropped down the tube and fresh soaked gauze applied to the raw surfaces. When the treatment is commenced some days or weeks after the infliction of the wound it is again necessary to open up all sinuses and pockets so that the fluid may reach all the septic areas, and if necessary tubes should be inserted so that free drainage is established. The fluid is then used in the same manner as previously. It is noteworthy that the fluid can be handled freely without doing any harm to the skin, but if left for a prolonged period in contact with the patient's skin around the wound a certain amount of burning may be caused. For this reason surface dressings should be formed of dry gauze. It is rarely necessary to smear the surrounding skin with sterilized vaseline. The following claims are made for the treatment: It overcomes sepsis more rapidly than other methods. With its use amputations are much less frequent. It diminishes pain rather than increases it as is so often the case with other dressings. The dressing requires to be changed only at long intervals. Its use is associated with no danger. The amount of work in the ward is greatly diminished. It is most suitable to the conditions of modern warfare.

Tissue Fragments and Wound Infection.—TAYLOR (*Ann. Surg.*, 1916, lxiv, 641), in connection with his military hospital work in France, carried out a series of experiments on guinea-pigs to determine the parts played by missiles, fragments of clothing, and detached or severely

traumatized tissue fragments, in carrying loads of bacteria and acting as foci of infection. The result of the experiments suggests that in the cleaning of fresh wounds at least as much care should be exercised to remove separated and devitalized fragments of tissues as is taken to remove other foreign bodies. In all operative procedures where blunt dissection is practiced it should be remembered that torn fragments of devitalized tissue may remain to become a ready soil for the incubation any bacteria which may gain access to the wound.

Blood-pressure and Graphic Vasomotor Changes in the Periphery During Ether Anesthesia.—Muns (*Ann. Surg.*, 1916, lxiv, 645) says that in a former paper he studied the changes occurring in the peripheral vessels during shock brought on by intestinal trauma. The animals used were anesthetized with ether, and the question arose as to what depressing, exciting or neutralizing effect the anesthetic may have had on the vasomotor mechanism. He carried out a series of experiments on dogs to study these effects, with the following results: Ordinary third-stage ether anesthesia prolonged beyond one hour results in more or less marked vasodilation in the periphery. This is a progressive change, more or less regular in character, increasing directly in proportion to the lengthening time of administration. In most cases the limit of vasodilation is not reached seven hours after the beginning of the anesthetic, but occasionally the extreme of the condition may be reached after a shorter administration of ether. There is a direct relationship between the condition of the vasomotor control and the blood-pressure. The end-result of ether depression is loss of function. The symptom-complex, known as post-operative shock, is a combination of the effects of excitation and depression, and varies direction with the algebraic sum of these two factors. The vasomotor center is the variable factor in bringing about the vasomotor change; the variation of response is directly dependent upon the changes in the vasomotor center produced by ether.

Blood-pressure and Prostatectomy.—Peacock (*Ann. Surg.*, 1916, lxiv, 659) says that there is a vital and definite relationship between the vascular system, and the renal functionating which is measured by the blood-pressure. And as old age and obstruction of the lower urinary tract greatly raise this pressure, we view with interest anything which suddenly decreases it, as serious complications often result. On the basis of seven prostatectomies in which blood-pressure observations were made, he found that there is a definite physiologic relation existing between the blood-pressure and the filtration in the kidney glands. That a high blood-pressure is purely compensatory, and necessary to the individual in which it is found, to maintain a normal excretion of urine. That any sudden and permanent lowering of the blood-pressure by radical or heroic measures is often a fatal procedure. That a persistently high blood-pressure, even in the absence of albumin and casts, usually means a hidden nephritis. That a chronic prostatic obstruction produces serious back pressure changes in the ureters, the kidney substance, the kidney circulation and the excretion of urine. That a sudden relief of this intravesical pressure produces an immediate fall in blood-pressure, from 20 to 100 mm. Hg. That if the pre-operative blood-pressure is much over 150 mm. Hg, the risk of a cystotomy or

prostatectomy increases rapidly. That compensation between the blood-pressure and the urinary excretion will take place if the pressure is not abnormal and will occasionally in a high pressure where there is unusual vitality or compensatory power.

Spondylitis Deformans Relieved by Albee Operation.—Finkelstein (*Ann. Surg.*, 1916, lxiv, 713) says that of all the ills that man is heir to, none can claim priority over spondylitis deformans as a deforming and disabling disease, not only because of its chronic progressive nature, but also because of our inability either to check its progress or to relieve its distressing symptoms. The spondylitis in this case began with a severe injury of the spine, twenty-eight years before operation, but it was not until twenty-two years later that working became a hardship. For five years he received non-operative treatment, including the use of a plaster cast. The Albee operation was performed in April, 1915, in the usual manner. The cast was discarded during August, 1915, and he began to work in an ammunition factory. He has been seen once every three months since. He is absolutely free from pain, and there is very little restriction of motion in spite of the fact that his work is very laborious, consisting of carrying shells weighing up to 50 pounds. He has not lost a day during the year. This is the first time, in Finkelstein's knowledge, that the Albee operation has been done for spondylitis deformans, and in view of the results obtained, he believes it has a distinct indication in (1) those cases where the disease is localized, (2) in the early stages before the disease has progressed, (3) where there is an acute exacerbation in a chronic process, (4) where there is abdominal breathing which is interfered with by spinal brace or spinal cast, (5) as a last resort in those hopeless cases where all other methods have been tried and found wanting.

Felons.—Dorrance (*Ann. Surg.*, 1916, lxiv, 716) says that he has 47 cases on file since his last paper on this subject, followed from beginning to end. Of these, 40 cases were opened within the first forty-eight hours, and complete cure ensued. Of the other 7, 5 were done after fifty hours had elapsed. Of the first two series the results were better than he has seen from longitudinal incisions, and of the last 2 cases, one had to have the phalanx removed while the other recovered only after a long and tedious treatment with a deformed finger. Dorrance makes an incision starting at the base of the nail on one side and extending in the line of the furrow over the tip of the finger, down on the other side to a point on a level with the beginning of the incision, in that way making a flap of the tip of the finger. It can be dogmatically stated that if the procedure is followed out properly, observing the rules, loss of sensation in the tip of the finger never occurs and the final result will be practically a normal finger. He concludes that all felons are caused by puncture wounds. Cases must be treated within forty-eight hours to get a perfect result. Cases over seventy-two hours' standing have usually damaged bone. Nitrous oxide is advisable in the majority of cases. The length of time required for perfect function depends upon the time elapsing before treatment is instituted. Restoration of function is quicker by this method than any other tried in Dorrance's experience.

THERAPEUTICS

UNDER THE CHARGE OF

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A Critical Study of One Hundred and Twenty Cases of Late Syphilis.—Wile and Elliott (*Jour. Am. Med. Assn.*, 1916, lxvii, 1916) present this study with particular reference to the effect of early treatment upon the development of late manifestations of syphilis. A definite history of treatment with particular regard to time of inception and character was obtainable in all the cases studied. Fifty-five cases had absolutely no treatment whatever. In the remaining sixty-five treatment had been inefficient except in one single case. In other words, but one case of the entire group had had what would be deemed, under the accepted criteria of today, intensive treatment. To sum up these figures, almost 50 per cent. of the cases had received no treatment whatever, and of the remaining cases in which treatment had been administered, with the exception of a single case of precocious malignant syphilis, the treatment had been desultory and unintelligently carried out. Inasmuch as it was found that over 30 per cent. of the cases occurred before the end of the fourth year, it seems fair to compare this series with a number of other cases which had been observed over the same period of time and in which treatment had been instituted at the outset and carried through intensively. Of such cases they had forty which they have been able to follow for the four years following their infection. These patients have all received repeated injections of salvarsan followed by vigorous mercurialization in the form either of inunctions or injections. Of this number, 36, or 90 per cent., have reached the fourth year without any signs of recurrence, and the largest percentage of these cases are serologically cured. Of the 4 cases in which there has been recurrence, two patients have returned with central nervous system involvement in the nature of neural recurrences which yielded promptly to treatment. One patient had recurrent mucous patches, notwithstanding vigorous treatment, and the last was the precocious malignant syphilid mentioned before. By far overshadowing all other causes of the appearance of late syphilitic sequelæ, the lack of, or inefficiency of treatment during the early period stands out as the most important factor. The inefficiency of treatment by the ingestion of pills is suggested by the fact that in some cases in which treatment was given the largest number had been treated in this fashion. The tendency for late sequelæ to appear increases up to the fourth year, which represents a fastigium after which there is a decrease in the probability. That no latent untreated cases are immune is suggested by the lapse of forty-four years after infection in one of the cases. Trauma probably plays a smaller role in the production of active syphilis during the period of latency than is generally supposed. Where it occurs it is likely

to influence the appearance of gummatous lesions in or around the skeletal structures. Intensive treatment as accepted by modern methods (salvarsanization and thorough mercurialization during the early months) is protective in the largest percentage of cases. In treated cases the occurrence of late sequelæ, except for isolated and exceptional cases, must be regarded as an indictment against the method of treatment.

The Control of the Nausea and Vomiting of Pregnancy by Intramuscular Injections of Corpus Luteum Extract.—Hirst (*Jour. Am. Med. Assn.*, 1916, lxvii, 1848) presents the results of further experience with the use of corpus luteum extract as a therapeutic measure for the nausea and vomiting of pregnancy. Hirst has now treated 25 consecutive cases, without any attempt to choose the favorable or eliminate the unfavorable. Corpus luteum extract injected intramuscularly was successful in controlling the nausea and vomiting in 21 of the 25 cases, and in four it proved a complete failure. The smallest number of doses in any successful case was four. The largest number of doses was forty-two, but the nausea had ceased after the tenth dose in this case. The dosage depends upon the severity of the symptoms. The remedy as used by Hirst is in the form of ampules, each containing one-third grain of soluble corpus luteum powder in 1 c.c. of salt solution, saturated with chlorbutanol for its local anesthetic effect. This amount is equivalent to $2\frac{1}{2}$ grains of dessicated gland. The injections have not produced abscesses and there have been no untoward symptoms following its use. Hirst believes that the effect of corpus luteum as a factor in controlling the nausea of pregnancy has not received the attention it deserves and hopes that a more extended trial will sustain his belief in its efficacy as a therapeutic procedure.

The Incidence and Treatment of Entameba Histolytica Infection.—Dobell (*Brit. Med. Jour.*, 1916, 2914, 612) compares the results obtained by treating amebic dysentery by subcutaneous injections of emetic hydrochlorid with those obtained by the oral administration of emetin bismuth iodid. Emetin hydrochlorid was given by subcutaneous injection to a group of 21 cases of amebic dysentery. The dosage for each patient varied from eleven to fourteen daily injections of one grain each. The stools were frequently examined during the treatment and for considerable periods of time after the completion of the treatment. Of the 21 patients thus treated, 7 were apparently cured, 5 were not even temporarily freed of amebæ and the remainder all promptly relapsed. In those cases relapsing the amebæ were again found in the stools at intervals of from one to sixteen days after the treatment was discontinued. Eleven of the 14 cases that failed to respond to emetin hydrochlorid were then given emetin bismuth iodid by mouth in doses of one grain three times a day for periods of twelve days. Everyone of these patients was promptly and apparently permanently cured. There were no untoward symptoms that followed the use of the drug by mouth except nausea in a few instances. The 3 remaining cases that had previously relapsed after treatment by emetin hydrochlorid were treated by a second course of the same preparation in daily doses of one

grain. Two of these were not even temporarily benefited by the treatment, while the third was freed of the amebæ for only three days and the infection then recurred. Two of these same 3 patients were then given emetin bismuth iodid and both were completely cured. Dobell then tried the effect of the remedy on a series of ameba carriers and a prompt cure was obtained in all. He believes that it is the most efficient remedy for carriers—affecting the encysted form of the parasite more certainly than does emetin hydrochlorid. It is interesting to note that many of the patients were infected with other parasites: Entameba coli, lamblia and chilomastix, and in no case were these parasites removed from the feces by any form of emetin treatment. The entameba coli disappeared during treatment in some instances, but promptly recurred after the discontinuance of the treatment.

The Quantitative Effect of Salvarsan on the Wassermann Reaction of the Blood.—King (*Jour. Am. Med. Assn.*, 1916, lxvii, 1669) says that in most cases little change occurs in the strength of the Wassermann reaction during the first five days following the administration of salvarsan. In a series of twenty treatments, only 1 case, in the primary stage, showed a marked weakening of the test. Some previously untreated cases may be given prolonged salvarsan therapy with very little weakening of the Wassermann reaction. Such cases may, however, show striking improvement symptomatically. In this series only one insignificant temporary increase (provocative reaction) in the complement-binding substance could be demonstrated, following the administration of salvarsan, The author thinks it is improbable that over short periods of time, there occurs any marked spontaneous fluctuation in the amount of complement-fixing substance in the blood of syphilitics, Definite proof of the existence of the provocative Wassermann reaction following salvarsan is not at hand at the present time.

A Further Report on Thromboplastin Solution as a Hemostatic.—Hess (*Jour. Am. Med. Assn.*, 1916, lxvii, 1717) has found that tissue juice made from brain (thromboplastin solution) has proved itself of practical value in controlling hemorrhage wherever it can reach the site of bleeding. In cases of true hemophilia it may be regarded almost as a specific hemostatic. It is to be recommended for local use in the bleeding of the newborn, in nasal hemorrhage, and in the parenchymatous bleeding associated with various operations. Where local applications fail, it should be injected into the site of hemorrhage, as in bleeding from the gums following tooth extraction. This method can readily be resorted to, as thromboplastin solution loses but little of its potency as the result of dilution and cursory boiling. Further clinical experience is necessary before its value can be determined as a hemostatic in connection with hemorrhage of the gastro-intestinal tract. However, it is innocuous when given by mouth in considerable dosage, and would seem to be indicated in bleeding from the stomach and from the upper intestine. Hess says that, in addition to its hemostatic action, this tissue extract has been found to possess healing properties, actively stimulating granulation tissue and hastening epithelization. It is therefore applicable as a dressing for torpid ulcers and sluggish wounds.

PEDIATRICS

UNDER THE CHARGE OF

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The Neuropathic or Nervous Child.—E. B. AUGELL (*New York State Jour. Med.*, 1917, xvii, 13) in a discussion of the nervous child quotes Dr. Francis Warner's description of the typical signs of the nervous child. Nervous children are apt to complain of headaches, are poor sleepers and hard to put to sleep, talk in their sleep and grind their teeth, and are tired on arising. They are delicate without having any disease and are rarely attacked by illness. They are not strong, cannot walk far without tiring; some days they are too tired to do anything and must rest. Their appetite is capricious and they easily loose weight. They are generally well made in body, but may be tall and rather thin, with subnormal body weight. In nerve signs they give evidence of weakness and overspontaneity. Augell lays emphasis on the study of the physiognomy and muscle action in the observation of children and suggests a well tried out test employed by Dr. Warner. In asking a child to extend its arms in imitation of your own example, the arms should come out parallel, hands almost on a level, fingers when extended are curved slightly downward from the wrist with the thumbs closely applied to the hands, a position which denotes the balanced action of a normally acting brain. The nervous child, however, shows a different result. If tired, there is drooping of one arm below the other, the thumb drops away from the hand and in extreme cases the hands drop from the wrist. If the nervous system is in a tense, unbalanced condition the fingers are overextended with the knuckles inclined slightly backward marking overmuscular action. This sign was noted in 25 per cent. of the author's cases. Augell is inclined to regard nervousness in children as dependent on ill-balanced nervous control rather than exhausted nervous energy. The relation between muscular and brain activity is very direct and Augell impresses the value of trained muscular exercise in increasing the size of the motor convolutions of the brain as well as the depth of the cortex and in developing ready control and quick response in the mind. He cites military drill as exceptionally valuable in this respect and in developing self-control which is a vital factor in the treatment of the nervous child. Neurotic inheritance plays a more important part in childhood neurosis than in the adult type. In 80 cases of typically nervous children, 70 per cent. gave a history of neurotic inheritance. The arthritic diathesis is another important factor, about 30 per cent. giving a family history of arthritic trouble in the immediate ancestry. Among a list of physical conditions and abnormalities which cause nervousness Augell mentions bad oral hygiene, disorders of the digestive tract or faulty metabolism, especially a too high protein diet, and conditions due to bad ventilation in home and school.

Little's Disease.—Joseph S. Wall (*Arch. Pediat.*, 1916, xxxiii, 812) brings out the various conceptions held by different authorities on this malady, showing quite a diversion of opinion as to what class of cases of spastic paraplegia should be designated Little's disease. Spastic paralysis, because seen in infancy and childhood should not be classed as Little's disease solely for that reason. Wall states that Little's disease appears to represent cases of congenital spastic rigidity or paralysis having their origin before or during the act of birth from causes within the central nervous system, particularly the cerebrum and that this excluded the whole group of spastic paraplegias occurring during infancy as well as those paralyses dependent upon peripheral lesions. The causative factors are both prenatal and natal. Prematurity apparently is held to be the main general factor, whether the effects are due to undeveloped fibers in the pyramidal tracts of the brain or as the French writers believe, to syphilis either in the father or mother. However, prematurity in itself may be questioned as originating Little's disease since so many premature infants grow and develop into healthy beings. Next to prematurity, perhaps intimately associated with it among prenatal factors, should be placed syphilis. The French school has brought many arguments to prove that syphilis is the most common cause of the disease. Natal causes include hemorrhages from trauma during labor. Basal hemorrhages are usually fatal while those of the cortex permit of life and the consequent degenerations shown in Little's disease. Asphyxia neonatorum has been noted in from one-third to one-half of many of the recorded cases. It would seem difficult, however, to differentiate between asphyxia as a cause of hemorrhage and asphyxia as a result and symptom of hemorrhage which has preceded the state of suspended animation. The pathological changes causing the paralyses and spasticities taken collectively show hemorrhage, meningeal and cortical, defect degeneration and inflammation. Primary destruction or non-development of the brain surface is largely responsible for the production of the syndrome of Little. Early symptomatology includes spasticity of the extremities and trunk, inability to support the head or retraction of the head, incoördination of the upper extremities, asymmetry of the face, difficulty in attracting the attention of the eyes, strabismus, "choking sounds" and laryngeal stridor. Later on lack of proper development and infantile growth become apparent and the symptom-complex depended upon the degree of cortical involvement.

OBSTETRICS

UNDER THE CHARGE OF

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Cases of Apparent Appendicitis Complicating Pregnancy.—Van Trim (*Ann. de gynéc. et d'obst.*, 1916, xlii, 177) draws attention to the occurrence of symptoms in pregnant women precisely simulating those of

acute appendicitis. In the first a gangrenous diverticulum was found at operation while the appendix was normal In two other cases the symptoms were caused by suppurating dermoid ovarian cysts. The fourth patient had classic signs of sudden pain in the right lower abdomen, but at operation the cecum and appendix were healthy. A collection of blood was found extending into the iliac fossa behind and below the uterus and broad ligament. The case proved to be one of intra-uterine pregnancy and also ruptured tubal pregnancy. The fifth case was postpartum, and the symptoms were caused by the twisted pedicle with partially suppurating ovarian cyst. It is not uncommon in parturient and puerperal women to have bilateral pain described in the lower abdomen. Occasionally this pain is unilateral and can often be traced directly to the region of the ovary. In some patients this pain follows nervous or psychic shock and is attended by no physical symptoms. In making a differential diagnosis the obstetrician should remember that young women may have an acute infective process with normal temperature and without rigidity of the abdomen, the cardinal symptom being high leukocytosis and the complaint of pain. This pain may occur periodically, and may strongly simulate the pain of hysteria. Great help is obtained in diagnosis by the examination of the blood to determine the degree of leukocytosis present and the bacterial examination of the urine to determine the presence or absence of colon bacillus infection of the kidney. Two cases in the experience of the reviewer illustrate this point. In the first, a young woman with a normal temperature was suffering from infection following a criminal abortion. She had no rigidity of the abdominal muscles and slightly subnormal temperature and rapid pulse. There was a foul discharge from the uterus. On admission to the hospital her condition was so grave that operation could not be performed. At autopsy rupture of the pyosalpinx and acute infection of the peritoneum were present. In a second case a young woman had produced upon herself abortion by inserting a slippery elm stick. She had a normal temperature, not much abdominal rigidity, but complained periodically of severe abdominal pain. Her leukocytes were above 21,000. The pain was so pronounced and came so regularly that it seemed hysterical in character. On section both Fallopian tubes exuded pus, the general peritoneum was injected, and the appendix was normal. This patient did well with drainage of the pelvic cavity.

Migrating Phlebetis.—Hedblom (*Jour. Am. Med. Assn.*, 1916, lxvi, 1777) reports the case of a woman, aged twenty-eight years, in her fourth pregnancy occurring during five years. The first two children had died of exhaustion, the third was living and well. At the end of twelve hours a fairly developed child was spontaneously born. There was no laceration and the placenta came away spontaneously. The uterus did not contract well and there was more than the usual loss of blood. On the eleventh day of the puerperal period the patient had severe night sweats followed by fever. The white blood corpuscles were 17,000, hemaglobin 60 per cent. There was inflammation of the right saphenous vein which gradually subsided. This was followed by inflammation of the other veins in the left side of the neck, axilla, arm and chest. This subsided to be succeeded by swelling in the other portions of the

body. In all the patient had six relapses, each attended by more or less severe constitutional prostration. The patient finally recovered and was discharged in the nineteenth week in good general condition.

The Combination of Morphin and Pituitrin in Labor.—Olivella and Arteaga (*Rev. méd. de Sevilla*, 1916, lxvi, 199) in 7 cases reported good results by using a combination of the hydrochlorate of morphin and extract of the fresh pituitary body and a sterile vehicle. Pain was greatly diminished, uterine contractions were better and the general condition of the patient remained good. Postpartum vomiting occurred in one case only and involution was normal. One child was born apneic, but was readily revived. The children seemed stupid and breathed languidly during the first twenty-four hours after birth, and required special care.

Joined Twins.—Iyer (*Indianapolis Med. Gaz.*, 1916, li, 237) reports the case of a woman who had been in labor three days. On examination a fetal head and left forearm had been delivered. A second head with its face turned toward the delivered one was also found. This could not be pushed up, so it was delivered with forceps without much difficulty. Both children were removed through the uterus and a common placenta was expressed shortly afterward. On examination it was found that the twins were attached by the cartilage of the ribs. There was a common abdomen covered only by peritoneum, but there were separate pelvic bones and pelvic organs. There was one cord and one liver and spleen. There were two pairs of kidneys, a single heart, one diaphragm, and two lungs.

Morphin-hyoscin Method of Painless Childbirth.—Haultain (*Brit. Med. Jour.*, October 14, 1916) states that the method of Krönig and Gauss had not been accurately followed by the majority of the British obstetricians who have used the drugs. In the Royal Maternity Hospital in Edinburgh, Haultain and his staff rigidly adhered to Krönig's technic in the first 8 cases and the results were satisfactory. He observed that patients sometimes became restless and highly excitable and this seemed to be a personal peculiarity of the individual case. With some patients more than twenty-two injections were given during labor. Where it was impossible to obtain separate rooms for the isolation of the patient, the ward was darkened and screens placed about the patient's bed and cotton placed in the ears. Forty cases were so treated, 36 primiparæ, and 4 multiparæ. The smallest number of injections was 4 and the greatest 45. Usually $\frac{1}{4}$ grain morphin was given at the beginning with $\frac{1}{150}$ hyoscin. In 3 cases $\frac{1}{6}$ grain morphin was first used. In 3 cases morphin was repeated and the second dose was $\frac{1}{8}$ grain. In 30 out of 40 amnesia and analgesia were obtained. There was some effect in every case. In 3 cases the method failed. In 1 case there was marked restlessness and injections had to be stopped. Postpartum hemorrhage occurred in one case and in 14 patients the forceps had to be applied. In 5 of these the instrument was used without chloroform and in the others chloroform was given. Of the 40 children, 5 were dead born, and of the 35 born living, 4 required artificial stimulation. In using the method in a primipara

the first injection must not be given too early, as it tends to stop the pains. When the os admits two fingers and pains are regular the drugs may be employed. In a multipara the injections can be begun as soon as labor starts. The second injection, $\frac{1}{150}$ grain hyoscin should be given about one hour after the first injection, and this can be repeated at intervals of one hour or three-quarter of an hour afterward. The morphin should not be repeated in the latter part of the second stage, because it tends to produce asphyxia in the child. The advice is given that if the hyoscin is not taking effect it is well to give the mother a slight whiff of chloroform. Thus the hyoscin is allowed to work and the patient passes into the condition of "twilight sleep." Thirty-seven of the 40 patients got up out of bed on the third day after labor. We are somewhat interested to observe that the writer describes the administration of morphin-hyoscin as the method of Krönig and Gauss. They employed scopolamin, and laid great stress upon the absolute purity and quality of this drug. There is nothing new in the employment of hyoscin with nervous patients whether they be pregnant or not, and morphin has long been known to be useful with nervous patients during labor. The suggestion to give chloroform to permit the hyoscin to take effect is an extraordinary method of treatment, and one which does not appeal to us. We do not observe that the results of this treatment were especially satisfactory in avoiding the use of forceps, and yet it is supposed that if the patient be spared suffering her strength will be conserved and the use of forceps will be reduced to a minimum. After being extensively exploited by the public press, and after a determined effort had been made to make the scopolamin method popular with the public, it has passed into the category of medical nostrums of doubtful value. The only benefit to the public and the profession which its attempted introduction produced was the study of the best and safest methods of lessening pain during labor, and this brought out clearly that the scopolamin-morphin method was difficult of application, uncertain in results, frequently producing asphyxia in the child, lengthening labor, and much inferior to other reliable and safe methods of treatment.

The Midwife Problem in England. — In the *Brit. Med. Jour.*, September 16, 1916, occurs the annual public health report of the city of London. This shows that the expectation of life for men and women is lengthened, especially in the case of women for all periods of life. The birth-rate diminishes steadily and is now 24.3 per thousand. The death rate 14.4 per thousand. The infant mortality rate is also lessening; 104 per thousand. Midwives are licensed and under control, but the compensation which they receive is so small that very few of them can rely solely on their practice as a means of livelihood. Some increase their incomes by keeping lying-in homes and others give instruction to pupils. It is estimated that 25 per cent. of the total births of London are attended by midwives. There is, however, a general tendency on the part of the midwives to call medical help more frequently. There is still considerable mortality from puerperal septic infection, 393 cases being reported, 113 of which proved fatal.

GYNECOLOGY

UNDER THE CHARGE OF

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Fatal Results of the Percy Treatment.—The method of treating inoperable uterine carcinoma by means of the so-called "cold iron" cauterization, advocated by Percy, has aroused much interest in this country in the past two or three years, and has been previously discussed in this department. So far, it has been practically impossible to get any definite statement of results from Dr. Percy himself, although he has been extremely enthusiastic regarding the possibilities of his technic, and a number of other surgeons have reported more or less favorable immediate results. As yet the method is too new to admit of judgment as to its ultimate accomplishment. That the immediate effects of this method of treatment may not be as devoid of danger as has been claimed is well shown, however, by a recent report from LEONARD and DAYTON, (*Surg., Gyn. and Obst.*, 1917, xxiv, 156) recording two postoperative deaths. The first patient was fifty-two years of age, and entered the hospital with an inoperable carcinoma of the cervix, with masses in each broad ligament. The uterus was cauterized for an hour by the Percy method, and then the point was introduced for a half hour into each broad ligament mass. In this, as in the other case reported, the full Percy technic (abdominal control of heat, ligation of internal iliacs, etc.) was carefully carried out. The patient developed symptoms of ileus, and died suddenly on the fourth day. At autopsy about 24 round ulcers were found in the stomach; there was a vesicovaginal fistula, and the tissues surrounding the cervix were destroyed, having a foul odor, and necrotic, putty-like consistency. Beyond this necrotic mass, however, perfectly preserved carcinoma was found. The immediate cause of death was a pulmonary embolus. The intestines were greatly distended, but no anatomical obstruction could be found. There were also pulmonary edema, hemorrhagic serous effusions, extreme cloudy swelling of the viscera, and renal epithelial necrosis—lesions which with the gastric ulcers presented a picture very similar to that seen after extensive superficial burns. It seemed possible, therefore, that death in this case may have been due, in part at least, to the same unknown factors. The second patient was about the same age, but entered the hospital with a very early carcinoma on one lip of the cervix. A typical Wertheim operation was done, but within six months she returned with a recurrence in the left broad ligament, which contained a firm, fixed mass about 5 cm. in diameter. This was treated by the insertion of the Percy cautery tip into the center of the mass, thoroughly heating it for two hours. The patient's condition was excellent for four days, when incontinence of urine developed and the temperature went up to 105°, eventually reaching 108°. Blood cultures showed streptococci, and on the sixteenth day the patient died. At autopsy a vesicovaginal fistula was found in this case, also, with a soft, gray necrotic mass of tissue extending out into the left broad ligament. At one point in the broad

ligament, just beyond the zone of coagulation, living carcinoma tissue was found. The cause of death in this instance was the streptococcus septicemia. From these two cases, the authors draw the conclusion that not only does the Percy method fail to kill off completely the cancer cells, but that it leaves a sloughing, coagulated mass of tissue which offers an ideal medium for the growth of microörganisms. It probably will be found impossible always to prevent infection of this area, and once infected the thrombosed vessels of the region offer a ready entrance into the system.

Syphilis of the Bladder.—Baker (*Surg., Gyn. and Obst.*, 1917, xxiv, 187) draws attention to the fact that while until quite recently this lesion was considered extremely rare, its very existence being denied by some authors, our increasing knowledge of urology has shown that syphilis will have to be given a more prominent place in the etiology of urinary disturbances. A sufficient number of authentic cases of bladder syphilis are on record to leave no doubt as to its existence, though no definite symptomatology has been established. It has been well said that syphilis is the great imitator, producing symptoms and lesions closely resembling those of many other diseases, and this is true of its vesical manifestations. The most common symptom is increased frequency of micturition, one of the most striking features being usually the extreme sensitiveness of the bladder, this being the more marked the closer the lesion, especially an ulcer, is to the vesical orifice. Urgency is always extremely marked, the symptoms thus resembling somewhat renal and vesical tuberculosis. The urine may show nothing but a few red blood cells, or may be frankly hemorrhagic; pus is usually absent, as are bacteria, and spirochete have never been found. The type of lesion found on cystoscopic examination varies according to the stage of the disease. In the secondary stage there may be small macules, or small multiple superficial ulcerations, with hyperemic mucosa. In the tertiary stage the lesions are of two types; the gummatous ulcer and the papillomatous tumor, both of which may exist together. These ulcers are usually single, with ragged indurated margins, grayish bases, and a surrounding zone of deep red color. The papillomatous tumors may resemble either carcinoma or the ordinary benign tumor; their surfaces are frequently ulcerated, and may be covered with incrustations. The most common site for both secondary and tertiary lesions is the base of the bladder, just external to the ureteral orifices but they may be found on any part of the wall. It is common to find the vesical orifice in females greatly swollen and irregular, or to find a gummatous tumor in this region. The tertiary lesions show no tendency to spontaneous cicatrization, but tend to progress to the point of perforation. The absence of ulcers, vegetations, etc., should not rule against the diagnosis of syphilis, however. Excessive swelling and hyperemia of the vesical mucosa, either diffuse or patchy, associated with the symptoms of a cystitis unresponsive to local treatment, the absence of all common etiological factors, and especially the absence of infection in the urine, with a positive Wassermann, and the prompt disappearance of all symptoms and lesions after antisyphilitic treatment should constitute, in the author's opinion, sufficient evidence for the diagnosis of syphilis of the bladder.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Typhus Fever.—S. B. GRUBBS (*United States Public Health Reports*, 1916, xxxi, 42, 2918) describes new methods adopted at the Boston Quarantine for destroying lice on typhus fever suspects. After undressing, the suspect is sprayed from head to foot with a gasoline soap solution. This is soap one, water four, gasoline four parts, to make the stock which is diluted with five to ten parts of water before using. After being sprayed he goes into a large shower bath and can be relied upon to wash the soap off thus saving the supervision usually necessary for unwilling bathers. Clothing is treated in a disinfecting chamber by a vacuum-cyanide method. The article enumerates some of the experiments that have been made. These demonstrate that lice can be killed not only in bundles of clothes but also in tightly packed and closed trunks. For this purpose a 20 inch vacuum is created in the disinfecting chamber, hydrocyanic acid gas from four ounces of sodium cyanide per one hundred cubic feet of chamber capacity is then introduced and left in for thirty minutes. The time may possibly be shortened by improved apparatus but as the handling of the clothing or baggage by the station force is unnecessary the greatest loss of time and trouble is eliminated and the owner has his possessions returned to him exactly as they were surrendered. This method presents the great advantage of not requiring baggage to be opened or even unlocked. As every piece must be unpacked and the contents sorted if steam or dry heat is used and besides this must be dried if immersed in insecticide solutions the advantage in handling large quantities of baggage is striking. As the process is entirely safe its application need not be limited to typhus fever suspects but may be used in lodging houses and similar institutions where it is necessary on account of vermin, to regularly disinfect the bedding and clothing of the inmates.

The Milking Machine a Source of Bacterial Contamination of Milk.—RUEDIGER (*Jour. Infect. Dis.*, October, 1916, No. 4.) made a study of the milk delivered to retailers in La Salle and Peru, Illinois, and found that milk which had been drawn by a milking machine almost invariably gave higher bacterial counts than those which had been drawn by hand. An investigation was made and milk drawn by hand from a cow into a sterile bottle. The milking machine was then used in the condition in which it was ordinarily kept, and also after the cups, tubes and cans had been sterilized by drawing a pailful of boiling hot water through them. The figures collected from this

investigation show that milk may be grossly contaminated by using an unclean and unsterilized milking machine. The water used for scalding should be boiling in order to be effective and immersion in a solution of "B. K." or chlorinated lime does not satisfactorily prevent the growth of bacteria.

Comparison of a Rapid Method of Counting Bacteria in Milk with the Standard Plate Method.—Frost (*Jour. Infect. Dis.*, September, 1916, No. 3) describes a rapid method of counting bacteria in milk. A comparatively low dilution of milk is made with nutrient agar, spread over a definite area on a microscopic glass slide and incubated only until the small colonies are visible under a compound microscope. The culture is then dried and fixed in the flame and stained with methylene blue, which is partially washed out, leaving the colonies a deep blue while the agar background is only tinged or quite clear. The counting is done under the low power of the compound microscope. Thirty-seven samples of milk, which varied in content from 675 to 20,000,000 bacteria per cubic centimeter, were compared. Each of these samples was analyzed by the standard method and by the rapid method, and the results obtained showed satisfactory correspondence between the two. With the exception of two samples all were placed in the same class by both methods. If the result obtained by the standard is taken as 1, the result with the rapid method was 1.6 for class A, milk with a bacterial count of from 0 to 10,000; 0.89 for class B, with a bacterial count of from 10,000 to 100,000; 1.9 for class C, bacterial count 100,000 to 1,000,000; 0.62 for class D, bacterial count 1,000,000 to 10,000,000. The number of bacteria obtained per cubic centimeter of milk varies with the magnification used in counting the colonies. Greater variations existed with the little plates than with the standard plates, because, under the higher power, groups of bacteria dead or not yet grown into colonies were counted. The necessary period of incubation for the little plates varies from three to twelve hours. With the little plates a much larger amount of milk is used than with the standard plates, hence the former method ought theoretically to be the more accurate of the two. The rapid method permits the examination of young colonies of bacteria and the recognition of individual microörganisms which is not possible by the standard method.

Comparison of the Rate of Multiplication of Bacteria in Raw Milk with the Rate in Pasteurized Milk.—Allen (*Jour. Infect. Dis.*, 1916, xix, 721) found that raw milk as compared with pasteurized milk exerts a powerful suppressing influence on the multiplication of certain bacteria. When Bacillus lactici-acidi is accustomed to the milk of a certain cow, apparently no killing of this organism takes place in freshly drawn milk. When a single cell of certain pronouncedly chromogenic kinds of bacteria is added to fresh milk, the organism is found plentifully in the milk after sixteen hours at 20° C., the injurious action of freshly drawn milk not being sufficiently intense to kill the one bacterial cell. After pasteurization the organisms which remain in the milk and those which are able to get into the milk find conditions more favorable for their rapid multiplication than before pasteurization.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Streptothrix in Bronchopneumonia in Rats Similar to That in Rat-bite Fever.—Through the work of Blake attention has been called to a type of streptothrix which is probably the infecting organism in rat-bite fever. Since this report there have been too few cases to finally establish the common nature of the infection for all. The question of the origin of the streptothrix in the rat still remains unsolved. TUNNICLIFFE (*Jour. Infect. Dis.*, 1916, xix, 767) brings forward evidence to indicate that the rat is a carrier of this infection and is subject to bronchopneumonia from this source. Chronic bronchopneumonia was encountered in 60 white rats and in 56 of these a filamentous organism was observed in smear preparations. Cultures of a streptothrix were gained from 20 of these animals. This streptothrix was pathogenic in a number of normal animals inoculated. The microörganism corresponds morphologically and culturally with the Streptothrix muris-ratti as described by Blake. The infected animal showed an increase in opsonins and agglutins for this microörganism.

Experimental Arteriosclerosis of the Aorta and the Coronary Arteries of the Heart.—KRYLOV (*Compt. rendus de la Soc. biol.*, 1916, lxxix, 397) experimented on rabbits with the object of verifying the work of several previous writers, who maintained that the feeding of cholesterin or of food rich in cholesterin to rabbits produced in them characteristic changes similar to those observed in atheroma in man. The author fed his rabbits yolks of eggs, varying from 182 to 198 grams in quantity, and cholesterin, varying from 40 to 50 grams; then let them rest two weeks to six months. During the period of rest, fats and lipoid substances, particularly the doubly refracting ones, accumulated in the deep portion of the intima which was divided into two parts; a compact layer poor in cells but rich in collaginous and elastic fibers with few muscular elements and no fat, and below this a varying but always considerable quantity of fats and lipoids. These substances in the liver, spleen, and bone marrow are absorbed during the period of rest; in the aorta, however, conditions exist which are particularly unfavorable to their reabsorption, a fact which plays an important part in the development of arteriosclerosis. The predominating cellular

elements of the layer rich in fats are phagocytes of cholesterin, which undergo fatty degeneration and final calcification. The author further established the fact that, as in human atheroma, the process extended from the aorta to the smaller arteries, especially the coronaries. Limited to certain parts of the wall in the large arteries, it often spread over the whole surface of the small arteries and extended even to their finest ramifications. It began in a thickening of the intima by a deposit of fat and doubly refracting lipoids under the endothelium and with increased deposit led to the narrowing of the lumen. In the thickened intima variable quantities of cellular and muscular elements appeared in the process of degeneration. A period of rest after feeding had the effect of increasing the cellular elements in the tissues infiltrated by fat. The elastic tissue played a large part in the encroachment of the areas and the thickened intima of the vascular wall became a permanent characteristic.

A Note on Experimental Nephropathy.—Stoddard and Woods (*Jour. Med. Res.*, 1916, xxxiv, 343). The endotoxins of streptococci isolated from meningitis, or staphylococci from osteomyelitis, and the poisons of Vaughan's split products of the tubercle bacillus were daily injected intravenously or subcutaneously into rabbits for twenty to twenty-six days. The rabbits were then killed and autopsied immediately. The kidney lesions consisted essentially in an epithelial degeneration of the first division of the proximal convoluted tubules, with thickening and edema of the protoplasm and loss of the cellular membrane between adjacent cells, a diffuse process bordering on protoplasmic disintegration leading to a finely granular débris in the lumen of the tubule. The cells of the ascending loop of Henle contained a granular yellowish brown pigment. The distal portion of the convoluted tubules remained normal. These lesions were observed following the action of the poisons of the tubercle bacillus. The staphylococcic and streptococcic endotoxins, prepared according to the technic of Macfayden, produced different lesions from those just described and consisted in vacular degeneration with transformation of the epithelial cells into a tubule resembling fat tissue. This process was seen especially in the proximal and middle portions of the proximal convoluted tubule. There were no membranous lesions; the glomeruli appeared normal except for occasional slight thickening of the capsular and capillary walls. These changes differed according to the duration of the intoxication; the treatment with tuberculous products lasted twenty days. Rabbits received several inoculations of cocci heated to 56°, and killed in physiological salt solution. The authors call attention to the fact, however, that the lesions produced by proteins extracted by Vaughan's method, differed from those reported by Longcope and Boughton.

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ORIGINAL ARTICLES

THE DISTURBANCE OF THE LAW OF CONTRARY INNERVATION AS A PATHOGENETIC FACTOR IN THE DISEASES OF THE BILE DUCTS AND THE GALL-BLADDER.

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The gall-bladder has a definite place in the physiological organization of the animal body. Like the urinary bladder it presents an ingenious but simple mechanical device, by means of which a continuous glandular secretion is transformed into a discontinuous elimination. The value of such a device is easy to see in the case of the urinary bladder; without its interpolation between the ureter and the urethra the continuously secreted urine would most unpleasantly drip continually from the body. An analysis of many other excretory processes in the body would readily disclose the presence of such a transformatory device in their mechanism, but we shall confine our present discussion to the secretion of the bile and the role of the gall-bladder.

While the secretion of the bile into the biliary capillaries is a continuous process the discharge of the bile through the common duct into the duodenum occurs only periodically. During the intervals between the periods of evacuation the bile is stored away in the then practically quiescent gall-bladder. We know a few facts which make such an arrangement appear to be advantageous

and physiologically desirable. It is an established fact that bile salts as well as pigment are reabsorbed from the intestines, to be stored up again in the gall-bladder. It is quite probable that the presence of bile in the intestines, at a time when it is not needed for a specific digestive action, is liable to exert some injurious influence. Its periodical storage in the gall-bladder presents therefore a protective functional advantage. Furthermore, the bile in the gall-bladder is a great deal more concentrated than that which is present in the system of biliary ducts. When therefore the intestinal digestion is in that state of digestion which requires the activity of the bile the intestine receives it by the aid of the gall-bladder at once in a concentrated form. The gall-bladder therefore is on the one hand the means of providing the intestines with bile in a concentrated form when it is needed for digestion, and on the other hand it may be the means of protecting the intestines or some of its function when the presence of bile might be injurious to them.

While we thus see that the periodical discharge of the bile into the duodenum and its storing up in the gall-bladder is a physiological and advantageous process, we ought to recognize that it harbors a pathological element, and that is stasis. Moderate continuous movements and exchange of composition of the body's material is conducive to a physiological healthy state of life; abnormal retardation and stasis lead to pathological disorganizations. As far as the gall-bladder is concerned we have to bear the following in mind: Bile even under normal conditions seems to contain often living pathogenic organisms. They may be brought there in various ways: By entering the common duct directly from the duodenum; by passing up from the intestines through the portal vein, and possibly also by elimination directly from the systemic circulation, because, according to Adami and several French observers, the circulation even in health contained such pathogenic organisms as the colon bacillus. As to disease, there is no doubt that during infection the systemic circulation is invaded by pathogenic microbes. For typhoid it is fairly well established that in nearly every case the blood harbors typhoid bacilli during the entire course of the disease. Nevertheless, even in typhoid, cholangeitis, and cholecystitis are comparatively infrequent complications. What prevents their frequent occurrence? Two elements are of importance in preventing the development of inflammatory processes in the biliary system, though even the bile contains living pathogenic organisms. One is the maintenance of normal vitality of the mucous membranes of the gall-bladder and the bile ducts; microörganisms prefer to settle and grow on tissues which lost their resistence. The other safeguarding factor is the absence of an abnormally prolonged stasis of the bile in the various parts of the biliary system. Bile stasis is of primary importance as a pathogenetic factor in biliary

diseases. Stasis in itself may lead to a lessening of the vitality of the mucous membrane, and both together are then liable to make the mucous membrane of the biliary system the seat of inflammatory processes of various degrees and kinds: Catarrhal, suppurative, phlegmonous, membranous, or gangrenous. Furthermore, the inflammatory processes, when not of a stormy and fatal character, lay the foundation for the development of cholelithiasis. Besides, stasis alone, even without the intermediary action of inflammatory processes, favors the development of biliary calculi

We thus see that the physiological quiescence of the gall-bladder harbors a pathogenetic element. However, the periods of rest of the gall-bladder, as they exist in normal conditions, give apparently no rise to pathological phenomena. These set in, when the stasis of the bile is abnormally prolonged, of a chronic or a recurrent nature. What causes such abnormally prolonged conditions of stasis?

The data which pathology presents us are derived chiefly from observations made postmortem or in surgical operations. The observed facts, briefly enumerated, are as follows: When the gall-bladder or the bile ducts are in a state of inflammation the mucous membranes are red, swollen, and the lumina of the ducts, which are thus narrowed, contain in addition some mucus which increases the difficulty for the bile to pass out of the biliary system. In some instances Vater's papilla is even found to be completely closed by a plug of mucus. These conditions undoubtedly are capable of producing bile stasis, of diminishing or completely stopping the discharge of bile into the duodenum. But this stasis is here only a secondary phenomenon, it is merely a result of inflammatory processes, processes which, moreover, are themselves mere reactions, that is, they are themselves mere secondary phenomena brought about by some primary cause. Is there a form of stasis which in itself may be the chief, or a contributory cause of some inflammatory processes in the biliary system? Or, to put the question in other words, may not conditions happen which are capable of converting the periodically occurring physiological quiescence of the gall-bladder into an abnormally prolonged quiescence and thus converting the physiological storage of the bile into a pathological stasis? That is the central point of the problem I wish to discuss in this paper.

But before this question in pathology can be answered, there is a physiological question to be discussed and answered. What is the nature of the mechanism which in normal conditions causes the stream of bile at one time to be emptied into the duodenum and at another time to be diverted into the gall-bladder? This question was hardly ever taken into consideration when dealing with the pathogenesis of the diseases of the gall-bladder.

I have previously compared the mechanism of the gall-bladder with that of the urinary bladder. Of the latter we know that the

collection and evacuation of the urine is controlled by the antagonistic activities of two muscles of the bladder. During the accumulation of urine in the bladder the detrusor muscle is relaxed and the sphincter is tonically contracted, while the reverse takes place during evacuation, the detrusor contracts, and simultaneously the tonus of the sphincter becomes inhibited.

I could now apply directly the phenomenon of crossed innervation which we find in control of the activities of the bladder, without much discussion to the mechanism which dominates the activities of the gall-bladder. But I prefer to discuss here the phenomenon of antagonism from a broader point of view. The law of contrary innervation is manifest in all functions of the animal body, and I believe that a *disturbance of this law is a factor of more or less importance in the pathogenesis of many disorders and diseases of the animal body.* A better appreciation of this law, which can be brought about only by an insistent discussion of it, will render a service to pathology and clinical medicine. Thirty odd years ago I directed attention to the general principle that impulses inhibiting the action of antagonists must be an integral part of any kind of a movement in the animal body. For instance, simultaneously with each contraction of the extensors an inhibition of any form of contraction of the flexors, and *vice versa*, must take place. Otherwise, normal locomotion, for instance, would be practically impossible. I have demonstrated then, and recently we have shown it again, that this principle is an integral part of the respiratory mechanism. A few years before my general statement was made, we discovered that this arrangement is strikingly present in the mechanism of deglutition: The contraction of the lower parts of the esophagus and of the cardia become inhibited as soon as the upper end of the canal of deglutition begins to contract. Bayliss and Starling, Joseph and Meltzer, and Cannon and his coworkers reported observations of a similar reaction in several other parts of the digestive canal. Bayliss and Starling found that local stimulation of some segment of the intestines causes a contraction above and inhibition of the intestines below the stimulated part. They called it then the law of the intestines. Evidently this is not merely the law of the intestines but a part of a general law. Sherrington studied brilliantly this law, especially in the relations of the antagonistic muscles of the lower extremities. These relations exist there in a mutual way, and Sherrington termed them the reciprocal innervation. On account of the distinguished position of the investigator and the brilliancy of his work, physiologists are more familiar with this term and are apt to employ it in their writings. It is, however, evident that this is inappropriate to cover all phenomena manifestly belonging to this category. There is, for instance, no such "reciprocal" innervations in the physiological peristaltic movements of all parts of the digestive canal; there is

always only an inhibitory impulse for the caudal part of the intestine simultaneously with a contraction in the cephalic end of it. I therefore designated many years ago all these relations by the more general term of the *law of contrary* innervation.

I wish to add that many years ago I defined intestinal and gastric colic as being due to a disturbance of the law of contrary innervation—namely, that the caudal end remains contracted and stationary while the cephalic end contracts and progresses forward. The volume between the two contracted limits becomes gradually smaller while the contents of this volume remains practically unchanged; hence the increasing tension which leads to the unbearable colicky pain. Nothnagel, who previously went on record for another explanation of the origin of colic, admitted that some forms of colic may indeed have their origin in the described disturbance.

Let us now turn our attention to the application of the law of contrary innervation to the mutual relations of the evacuation of the bile through the common duct into the duodenum and to its storage into the gall-bladder. I dwelt on this subject some fourteen years ago in a paper on "Inhibition." We know that the gall-bladder is well provided with muscle fibers, the contraction of which will free the gall-bladder from its fluid contents. As to the termination of the common duct, Oddi described some thirty years ago that the papilla of Vater is provided with circular muscle fibers which by their contraction close up the common duct. This contraction is strong enough to resist a pressure much higher than that which usually obtains in the bile ducts. It is clear that the muscle fibers of the gall-bladder and those of the papilla are antagonists. Applying our knowledge of the mechanism of the urinary bladder, and more generally the law of contrary innervation, the physiological mechanism of bile storage and bile discharge is quite simple. During the storage the muscle fibers in the papilla are contracted and those of the gall-bladder are inhibited; during the discharge the gall-bladder contracts and Oddi's muscle is relaxed; the bile has then no other way out but into the duodenum. The innervation of the concerned parts, although not yet settled in its details, is very interesting. According to Doyon, stimulation of the peripheral end of the splanchnic nerves causes simultaneously a contraction of the gall-bladder and an inhibition of the tonus of Oddi's muscle. The vagus, on the other hand, seems to contain motor fibers for the sphincter of the common duct and inhibitory nerve fibers for the gall-bladder. Furthermore, also the afferent innervations show the character of contrary innervation. For instance, stimulation of the central end of the vagus causes simultaneously a contraction of the gall-bladder and an inhibition of the sphincter muscle.

While the physiological muscular and nervous mechanism of bile storage and bile discharge is thus satisfactorily explained the

question presents itself: What are the causes which bring about either of the two actions? We compared the mechanism of the gall-bladder with that of the urinary bladder. But the latter is to a large degree under the management of the will, and the sensations of fulness and other sensory stimuli bring the condition of the bladder to the attention of our consciousness, which by means of the will sets the required part of the mechanism into action. The processes of storing of the bile or of emptying it never comes to our consciousness and are never managed by our will. What does then manage their proper activity? We must admit that we do not yet know a great deal about it. It is probable that certain conditions and certain substances exert a selective action upon the reciprocal reflexes. It is interesting to quote here some newer instructive statements. One comes from Pavlov's school. Bruno stated that no bile appears in the duodenum as long as the stomach is empty. When a meal is taken the entrance of chyme into the duodenum gives the signal to an ejection of bile from the common duct. Most interesting are the recent studies of Rost. He first established the fact that after cholecystotomy the escape of bile through the papilla of Vater is indeed continuous, which in normal animals it is always a discontinuous one, depending upon the entrance of food into the duodenum. He found, further, the instructive fact that injection of peptone or albumosis through a duodenal fistula in a normal dog causes immediately a discharge of bile from the common duct, and he has proved that this takes place by a reflex act which causes a contraction of the gall-bladder and simultaneously a relaxation of the sphincter of the common duct.

From the foregoing it seems quite safely established that the physiological discontinuous character of the flow of bile into the duodenum is regulated by a reflex mechanism, dominated by the law of contrary innervation; that the integrity of the gall-bladder is an important part in this reflex mechanism; that the discharge of bile can be greatly curtailed by the absence or a restriction of the discharge of chyme from the stomach into the duodenum, and that the discharge of bile through the papilla of Vater into the duodenum is greatly enhanced by the presence in the lumen of the latter of peptone or albumosis.

We return now to our original question in pathology, which was this: May not, by some functional disorder, the physiological storage of bile be converted into a pathological stasis and thus become the cause of a more or less serious ailment of some part of the biliary system? I am inclined to answer this question in the affirmative. We are confronted with many possibilities to which I see no objection, derived either from theoretical considerations or from practical observations. The mechanism of bile storage and of bile discharge is depending on such a fine nervous adjustment that we can readily conceive a disturbance of it without the presence

of a concomitant palpable anatomical or chemical disorganization which played and still plays an all dominating pathogenetic role in pathology and medicine. We need, for instance, only to assume that by some mental excitement the tonic contraction of the sphincter of the common duct, at the period assigned for the discharge, does not become relaxed while the gall-bladder contracts within the usual normal limits; this would result in abnormal stasis within the biliary ducts which may lead to icterus—*emotional icterus*. Or both the muscle fibers of the gall-bladder and of the sphincter are abnormally strongly contracted, which would lead to biliary colic with consecutive jaundice without the presence of catarrhal conditions or of calculi, at least not in the first few attacks of comparatively short duration. When such disturbances occur often and are of longer duration these attacks of primary pathological biliary stasis may sooner or later lead to inflammatory processes and their consequences or to the formation of biliary calculi. Such conditions may set in sooner and readier when the individual passes through such infectious diseases of which we know that during that period the circulatory blood as well as the bile contain the causative organisms. Besides psychical influences (and perhaps disorganized internal secretions which are conducive to a disturbance of the emotional equilibrium) there are the influences of the partaking of food and of the character of the food which is partaken which may prove sooner or later to be pathogenetic factors in the formation of biliary diseases. Continuous fasting for many days, or even weeks, may be of lesser significance, since the consecutive stasis may be corrected by a gradual absorption of the stagnant bile and a great reduction or complete cessation of secretion of new bile. But simple infrequent feedings, say the partaking of only one meal or even two meals a day, may very gradually finally lead to pathological consequences. The accumulation of the bile in the gall-bladder and in the ducts for longer periods, and the continued repetition of these periods may gradually reduce the normal resisting power of the corresponding mucous membranes which may become a serious pathogenetic factor, in case the individual has passed or is passing through an infectious disease. Furthermore, taking the above-mentioned experiments of Rost in consideration, the abstaining from taking proteins or partaking them infrequently or in minimum quantities may prove to be another factor in the pathogenesis of biliary diseases.[1]

[1] About a decade ago feeding experiments were conducted by Chittenden on a squad of men to prove the fact that the high dietary calories, as required by Voit and his followers, were unjustifiable and that men and animals may show a normal metabolism and be apparently in perfect health even when partaking of only small amounts of proteins. In my paper on the "Factors of Safety" I objected to the conclusion that the minimum amount of food which shows no immediate palpable evil results is the ideal diet; the minimum should not be identified with the optimum. It is perhaps worth while to record the fact *that one member of the above-mentioned squad*

As stated above, we do not know yet sufficiently about the physiology of bile storage and bile discharge. Bile secretion and the actual physiological effect of bile I have not taken at all into consideration in the present discussion. When we shall know more of the physiology of the mechanism we shall know a good deal more about the pathology of biliary diseases. I belong to those who believe, and often said it in print, that the knowledge of physiology and an understanding of its disorders is of special importance to clinical medicine. Pathological anatomical changes are often only the result of a disease and are of a static nature and unchangeable. Physiological changes are of a dynamic nature, are often reversible, and clinical medicine has well-founded reason for the hope that by perseverent, intelligent research we shall gradually find more and more remedies and ways by means of which we shall be able to reverse various diseases—to cure them. In this paper I attempted to show that there is a general physiological principle which I termed the law of contrary innervation, which plays a leading part in the mechanism of storage and discharge of bile and that a disturbance of the fine adjustment may be a pathogenetic factor in various biliary orders. I have also shown further that very infrequent feedings and especially the avoidance of food which is capable of sending to the duodenum peptones and albumosis may lead to a pathological biliary stasis.

From these considerations it follows that even in health it is advisable to partake comparatively frequent meals, although they need not consist of large quantities, and that the meal shall contain foods which readily send peptone and albumosis into the duodenum. This principle ought to be especially observed in infectious diseases during which the bile contains the causative organisms. In typhoid, for instance, food should be administered every two hours and the food should contain materials which may readily be converted into peptone and albumosis. The frequent elimination

who followed out the minimum diet more conscientiously than any other member, and for a longer period, had the misfortune to pass through an attack of typhoid fever. For the last few years he complained of pain in the region of the liver, and recently was operated on for gall-stones. Another faithful member of that squad has been complaining for several years of indigestion and of pains in the right upper quadrant. I am not familiar with the details. I understand the trouble was diagnosed as duodenal ulcer. We are reminded of the dictum of William Mayo: that when there is trouble in the right upper quadrant only a laparotomy will reveal the exact cause of the trouble. I have not followed out the fate of the other men of the experimental squad who, by the way, did not seem to be overzealous in the performance of the experimental diet, nor did they follow it out longer than they had to. It is apparently insufficient to draw final conclusions from the *immediate* effects of a definite experimental diet; the fate of such individuals ought to be followed out for many years. What effect the "meatless days" and other dietary instructions may have in the future upon the races of belligerent Europe cannot be learned at present from the proficiency in school work and other immediate effects. The future might provide us with unexpected lessons, if we are alert enough and willing enough to connect events occurring so far apart.

of the bacteria-laden bile may be the means of preventing the development of cholangeitis and cholelithiasis. The direct administration of peptone in capsules may be useful in infectious disease as well as in some of the biliary disorders.[2]

THE DIAGNOSIS OF GALL-BLADDER DISEASE.[1]

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During the four years 1912, 1913, 1914, and 1915, detailed records were made of 1708 patients who presented themselves for diagnosis and advice. All of these came because they had some disorder of internal organs, most of them of the digestive organs. Among these 1708 cases there were 56 in which a diagnosis was made of disease of the gall-bladder; and a study of these shows not only the forms of gall-bladder disease commonly met with, but the variations of each form likely to occur.

I. Chronic Cholecystitis. Probably chronic cholecystitis always precedes cholelithiasis. Gall-stones form, according to present day opinion, because infection of the gall-bladder mucous membrane, increased secretion of mucus, desquamation of epithelial cells, and excessive production of cholesterin make their formation possible. There may still be room for discussion as to whether microörganisms enter the gall-bladder from the intestine, along the bile ducts; or from the blood stream, excreted into the bile from the liver. There may be reason for doubt as to whether colon bacilli, typhoid bacilli, streptococci, or staphylococci most often cause the infection. But there seems no reason whatever for skepticism as to the fact that low-grade infection of the gall-bladder and chronic inflammation so

[2] According to the view taken in this paper some cases of jaundice and of biliary colic have their origin in the fact that the sphincter of the common duct is abnormally contracted and does not become relaxed, as it physiologically should, during the contraction of the gall-bladder. In experiments with magnesium sulphate I observed that the local application of a 25 per cent. solution of that salt upon the mucosa causes a completely local relaxation of the intestinal wall. It does not exert such an effect when the salt is administered by the mouth, that is, when it has to pass through the stomach before it reaches the intestines. The duodenal tube, however, apparently has reached an efficient practical stage. I make, therefore, the suggestion to test in jaundice and biliary colic the local application of a 25 per cent. solution of $MgSo_4$ by means of the duodenal tube. It may relax the sphincter of the common duct and permit the ejection of bile and perhaps even the removal of a calculus of moderate size wedged in the duct in front of the papilla of Vater. Twenty-five cubic centimeters of the solution as a dose for an adult will bring no harm. For babies the dose should not exceed 4 c.c. The procedure could be developed into a practical useful method.

[1] Read before the Stanislaus County Medical Society, at Turlock, Cal., September 8, 1916.

induced underlie the formation of gall-stones. It follows, therefore, that a variable period must elapse of weeks, months, or even years during which chronic cholecystitis exists but cholelithiasis does not. In fact, no positive clinical evidence is ever furnished that gall-stones are present until they attempt to escape, giving rise to the dramatic set of events known as biliary colic. Before the occurrence of an attack of such characteristic pain, no other diagnosis can be made than that of chronic cholecystitis; and even after such attacks no gall-stones may really be found at operation because the same biliary colic may be caused by acute exacerbations of the chronic inflammation, with blocking of cystic and common duct by inspissated bile and by spasm. The symptoms that precede such attacks of pain, whether the pain be caused by stone or not, are the symptoms of chronic cholecystitis, and should be recognized before biliary colic calls attention unmistakably to the seat of disease. What then are the facts in the history and physical examination of any case that justify the conclusion that chronic cholecystitis exists? In the series of cases observed, this condition was diagnosed 17 times. In 8 of these operation was done and in 7 the diagnosis was verified; while in the remaining case that came to operation no disease of the gall-bladder was found, but a chronic appendicitis. In the other 9 cases diagnosed there seemed as much reason for the conclusion as in the seven that were verified by operation; and a review of the 17 will therefore show what the basis is for such a diagnosis.

The symptoms of chronic cholecystitis are of two sorts: (1) *local*, pointing direct to gall-bladder; (2) *reflex* disturbances of digestion, suggesting the stomach as the seat of disease. Sometimes one group of symptoms predominates, sometimes the other; most frequently there is a mixture of both. The following case history calls attention particularly to the local manifestations. The patient, a young woman, aged twenty-six years, when seen first in January, 1912, complained that for six years previous she had had numerous attacks of pain in her right side, varying in severity, brought on by over-exertion, or by jarring, such as riding in an automobile. Between attacks she complained of a sense of weakness in her side; of a pulling down feeling there; of pain in her side on reaching up with her right arm; of something crowding her just at the right costal margin; and of inability to sleep with comfort when lying on her right side. Finally, in December, 1911, her pain grew worse than ever before, fever developed and for the first time she became very yellow all over her body, the fever and jaundice lasting for several days. She had a good appetite and no food distress between attacks, but a constant sense of beating and throbbing in her side and the whole side felt bruised and tender after the December attack, clear to her armpit. The only definite physical finding was great tenderness and rigidity along the right costal margin, most noticeable about half-way between the nipple line and the right sternal border. With

medical treatment this patient's discomfort grew somewhat less, she gained a little in weight and strength, but her side continued to feel weak and swollen and tender and "thumped" on any exertion. Finally in August, 1912, she had another attack of severe pain in her right side, with intense nausea, with fever for four or five days, and jaundice that persisted this time for weeks. Operation was advised for chronic cholecystitis, with recurring acute exacerbations but was not permitted until March 1913. At operation there was found great thickening of the gall-bladder walls, and the contents were as black and thick as tar, but no stones were present. Drainage of the gall-bladder resulted in relief of all symptoms.

The following clinical picture better presents the mixed manifestations ordinarily found. A young woman, aged twenty-four years, seen first in February, 1912, had been ailing for six years with recurring attacks of pain in her right side; had been operated upon for chronic appendicitis and her appendix removed, in Philadelphia, in 1909, but without permanent relief; then again in May, 1910, in San Francisco, after constant nausea and pain in her side high up, at the costal margin, and after jaundice for two months, she was operated upon for drainage of her gall-bladder, when chronic inflammation was found but no stones. She remained well after that until the following December, when she began to have constant nausea and frequent vomiting; distress soon after food and a feeling of great fulness; dull aching pain localized on the right side up underneath the ribs, radiating under the right shoulder-blade, increased by exercise or any jarring such as horseback-riding; and inability to raise the right arm to pull a window down or to reach for anything on a shelf, without increasing her pain in the right side at the lower border of the ribs. Physical examination showed great tenderness at the spot where she felt her pain and very decided rigidity there; while stomach analysis proved that her digestive symptoms were due to a hyperchlorhydria. Further operation was declined; and while her condition was improved by diet and drugs, it was never restored to normal.

The local evidences of gall-bladder disease may be so pronounced as to speak for more than cholecystitis. As showing this resemblance of chronic cholecystitis at times to cholelithiasis and the difficulty in deciding whether the latter condition has really developed as a sequel, the following history is characteristic. A man, aged fifty-six years, seen in August, 1912, began five years before to have recurring attacks of pain and soreness in his upper abdomen, at first coming on months or weeks apart, but recently almost constantly, with only a few days' interval between; and at times these attacks had been severe enough to require an opiate for relief. Jaundice had come for a year past after every attack of pain, but usually lasting for only a few days. His appetite was very poor, all food caused distress, and he had lost 30 pounds in weight in the last year.

This man's physical examination was absolutely negative except for the evidences of moderate icterus in eyes and skin, with no tenderness or palpable mass in the gall-bladder area. Nevertheless, at operation his gall-bladder was the size of a goose-egg, attached to surrounding structures by many adhesions, its walls very thick, and its contents consisted of about two ounces of dark, tarry, viscid bile. No stones were found, only a few particles of coarse sand.

Even more puzzling is the following history, in its resemblance to that of gall-stones: A woman, aged forty-five years, seen in February, 1914, complained of pains in the right side of her abdomen, at the lower border of the ribs; these had annoyed her for years past, but worse for the past two years, coming at least once in six months, and for the past four months much more frequently, as often as twice a week. The pain came suddenly, most often at night, at the border of the ribs on the right side and radiating thence to the back under the right shoulder-blade; was very severe and cramp-like in character, only relieved by opiates, leaving her sore and tender, for a day or two afterward. No fever accompanied and no jaundice followed. The patient was obese, but no physical abnormality was found except extreme tenderness and rigidity at the right costal margin, over the site of the pain. Operation showed a contracted gall-bladder, containing thick, tarry material, with several fine dark crystals, but no stones.

Many of the cases of chronic cholecystitis come for advice for "stomach trouble," the reflex symptoms of digestive disturbance causing far more annoyance than the local gall-bladder manifestations, which are often overlooked entirely until questioning brings them out. The following history is typical of this group. A woman, aged forty-seven years, seen first in February, 1914, said she had suffered for years from what she called "intestinal indigestion" until her appendix was removed in 1905, after which this trouble ceased. But for about five years past she had had trouble with her stomach, varying in degree but never gone. Her complaints were that all food caused distress, persisting at times for hours; much belching of gas; frequent nausea for weeks or months at a time; with dizziness and vertigo and weakness. Inquiry revealed the fact that her worst pain was felt in her right side, at the margin of the ribs, running around to the back and under her right shoulder blade. Many days at a time she had this pain, with throbbing and a sense of too great fulness. Once, in association with this constant pain, she became jaundiced for a week. Examination showed rigidity and tenderness at the right costal margin, with extreme pain when the Murphy maneuver was attempted. A test-meal demonstrated the existence of a decided hyperchlorhydria (total acidity, 72; free HCl, 32; combined HCl, 20). This patient, like many others, was so obsessed by her stomach symptoms that she could not accept at once the diagnosis of chronic cholecystitis, and insisted on medical treatment;

until finally, in May, 1914, she had a definite acute exacerbation, with chill, followed by fever, and intense pain and constant throbbing in her right side at the costal margin. This led to operation which revealed many adhesions about the gall-bladder, its walls thick and tough, its lining membrane granular and thickened and its contents very dark and muddy. No stones were found. The stomach was normal in every respect. This patient slowly regained her health following drainage, her dyspepsia disappeared, she regained her lost weight and is today in perfect health.

One other case, seen in July, 1915, also well exemplifies the gastric side of the cholecystitis picture. This woman, aged twenty-nine years, complained most of her stomach—of a ravenous appetite, but that all food caused gas and belching, with distress and pain, relieved by getting rid of gas; these symptoms going on for years past, but getting more severe all the time; with constant soreness over the stomach and progressive loss of weight. When questioned about them, this patient recalled recurring attacks of severe pain in the pit of the stomach, preceded by much gas and bloating, when she would have to remove her clothing for relief and put on hot applications; the pain was not colicky, and never lasted over an hour. These attacks went back as far as eight or nine years; at first they came only once in three or four months; but for the past two years they had gradually become more frequent, and for the past few months had come as often as every week or every few days. Also, for the past six months, she had had much aching pain, and at times soreness at the margin of the ribs on the right side, always worse after a ride in an automobile. This was constant but variable in intensity. Examination showed a very tender rounded mass in the region of the gall-bladder, descending on deep inspiration from beneath the ribs. A test-meal showed only a moderate grade of hyperchlorhydria. Operation the following November showed extensive adhesions of gall-bladder to colon and liver, burying it and binding it down; it contained very dark, thick bile, but no stones. The gall-bladder was removed.

All of the 17 cases diagnosed in this series as chronic cholecystitis, like those that came to operation, showed this combination of pain and discomfort in the gall-bladder region, with more or less disturbance of digestion. Errors in recognizing the real state of affairs arise on the one hand from considering only the stomach manifestations, or, on the other hand, from misinterpreting the gall-bladder manifestations and calling all cases cholelithiasis. One other possible error lies in attributing both the local and the reflex symptoms to appendix disease; but this, in the writer's experience, is less probable than the opposite error of diagnosing cholecystitis when the real pathology is appendicitis. As regards the patients themselves, it is remarkable how often their minds are fixed on their disturbance of digestion to the exclusion of all else; and unless the diagnostician

is alert, he will get no complete story of the condition. Examination of the stomach most often reveals hyperchlorhydria as a cause of the dyspepsia; but sometimes subacidity and sometimes complete achylia. But no evidence usually exists of organic gastric disease, unless as a complication, while the history and the physical signs point direct to the gall-bladder as the seat of the real disease.

II. Cholelithiasis. Stones may form in the gall-bladder and give no sign of their presence; the only symptoms being those already produced by the preceding cholecystitis. Such are the "inaugural symptoms" described by Moynihan as due to gall-stones, which frequently exist, even when ultimate operation shows no stones present but only a chronic cholecystitis. The clinical picture described as "biliary colic" is introduced into the history when a stone attempts to escape from the gall-bladder. Coincident with this event, either causing it or produced by it, an acute exacerbation is set up of the chronic inflammatory state; and it is difficult to say in any given attack how much of the symptoms are due to one or to the other. But the suffering caused by one of these attacks is usually so violent and excruciating, so far in excess of any previous effects produced by the gall-bladder disease, that now if never before the seat of the trouble is recognized and no longer doubt as to diagnosis can exist. In the series of cases here reported, cholelithiasis has been diagnosed 37 times; and in 20 of these operation has been done. In 17 by operation the diagnosis was proved correct; but in 3 no disease of the gall-bladder was found, while the real pathology was a chronic appendicitis. The cases of cholelithiasis with long intervals between attacks of biliary colic are loathe to accept operation, particularly if the intervals are characterized by fairly good health and freedom from digestive discomforts; hence the fact that out of 37 cases diagnosed, only 20 have come to operation. Many problems are presented, after all, in the recognition of cholelithiasis, because many variations occur in the clinical history, in the findings on physical examination, in the coincident gastric conditions and in the details of recurring attacks of biliary colic, even in the same individual. An account of some of the cases observed will best bring out the facts upon which we depend for diagnosis, and will show that there is no exact typical always recurring clinical picture.

A man, aged fifty-five years, seen in October, 1912, had his first attack of severe pain in the upper abdomen eight years before; and since then only three similar ones, lasting in each instance only a few hours at a time. In the interval between these he had occasional periods of indigestion, but much of the time no trouble at all. The site of his painful attacks was the pit of the stomach; the pain radiated through to the back, under both shoulder-blades, never around either side; was very intense, colicky and spasmodic, so that he felt at times as if he could not stand it any longer; it lasted a variable time, depending on his ability to get the opiate he required;

he never vomited during the attack and was never nauseated, but always perspired freely; never had been jaundiced after any attack, but was always left sore for several days in the pit of the stomach, not over his liver or right costal margin. His stomach trouble consisted of heaviness and fulness almost immediately after eating, with at times a dull pain; but no belching of gas, no heartburn or water-brash or nausea or vomiting. This man's stomach showed a decided hyperchlorhydria but no other abnormality; and his abdomen was slightly tender and tense at the right costal margin, but no palpable mass could be found there or elsewhere. For a long time he refused operation, convinced that his stomach was the seat of disease. Later on some of his attacks of pain were accompanied by chill and fever and the passage of very dark urine; the painful attacks grew more frequent in spite of medical treatment; he lost continually in weight and his indigestion became constant. Finally, in March, 1913, he submitted to operation. Many adhesions were found about the gall-bladder area, of the liver to the abdominal wall, of the gall-bladder to the duodenum and to the stomach; with one particularly strong adhesion between gall-bladder and duodenum, just beyond the pylorus, as if at sometime a stone might have perforated and escaped that way. The gall-bladder itself was very white, tough, and thick walled, and contained probably fifteen stones of varying sizes and shapes, old, hard, angular and with many facets.

The foregoing history shows how biliary colic may deviate from the orthodox text-book description. The pain was always epigastric, never radiated along the right costal margin, and was felt with equal intensity all over the back, beneath both shoulder-blades. Jaundice never accompanied or followed, neither was there vomiting. The man's own conviction, from his repeated spells of indigestion and the site of his painful attacks, was that his stomach was the primary seat of disease. Such a history might easily deceive, particularly in the absence of definite physical findings in the gall-bladder area and the presence of a persistent high-grade hyperchlorhydria.

Another common source of error is the impression that cholelithiasis occurs only in middle age or later. The following case demonstrates the incorrectness of such a belief: A woman, aged twenty-six years, seen in August, 1912, complained of stomach trouble. Beginning at the age of twelve years, she had repeated attacks of abdominal pain diagnosed appendicitis, recurring once or twice a year, until finally she was operated upon in 1908 and a purulent appendix removed. For a time after that she seemed well, but within a few months her attacks of pain in the upper abdomen began again, and she had had more of them during the past year than ever before. The attacks began with pain in the pit of the stomach, radiating usually up into the chest and not to the right side; this pain at times was very intense, and on some occasions required opiates; was colicky in character; came on frequently at night,

arousing from sleep; lasted for several hours unless an opiate was given; no nausea or vomiting accompanied and no jaundice had ever followed; there was some tenderness over the epigastrium at the time, but not afterward. As regards digestion, she complained much of heartburn, waterbrash, and sour stomach, but not of belching or nausea or pain. No pain was caused in the right side by jarring. This patient was well nourished, of good color, and no abnormality was found anywhere on physical examination, not even in the abdomen. The costal grooves showed no difference in tension, and there was no fulness or tenderness over the gall-bladder area. The stomach analysis was within normal limits and the stomach normal in size. Roentgen-ray plates revealed no abnormality. The history in this case was diagnostic, but there were no confirming signs. The patient, however, continued to have her recurring attacks of pain until operated upon in October, 1912, when the gall-bladder was found firmly adherent to the transverse colon, the pylorus, the duodenum, and in fact to all adjacent tissues; and it contained approximately 250 stones.

One grows accustomed after a time to the variations that occur in the story of biliary colic and can almost make the diagnosis of gall-stones by a careful history alone. There certainly is no more important element in the diagnosis than a painstaking, detailed account of the patient's attacks. Physical examination is often surprisingly negative in comparison with the pathology ultimately found; because the gall-bladder is tucked up beneath the ribs, where it is inaccessible to palpation. The history, therefore, becomes of great importance in any case, but as no two cases are exactly alike, there is, as before stated, no constant, unchanging clinical picture. The attack frequently begins at night, but it may begin at any time of day; the pain is usually located in the right hypochondrium, but may be most intense in the epigastrium or the left hypochondrium; usually it radiates along the right costal margin, to the back, under the right shoulder-blade, but may radiate instead directly through between the shoulder-blades, upward into the chest or downward into the abdomen; jaundice is not at all a regular accompaniment, and its absence is no bar to diagnosis; even when it occurs, it may be slight, transitory, and overlooked, while reflex symptoms, such as vomiting, may never occur at all. Fever may or may not accompany the attack of pain. No age is exempt from gall-stones, though they are more common in middle life; and they may occur in lean individuals, though more often in the obese.

The following is comparatively a typical history: A woman, aged fifty-one years, seen in July, 1912, began about five years before to have attacks of pain in the upper abdomen. These came once a month or even as often as once a week, but she might go two or three months without one. In the interval between attacks she felt perfectly well. Gradually her attacks had become much more

frequent; sometimes occurring every day or even twice a day. The attack came very suddenly and ended very suddenly; the pain was felt in the epigastrium and across the upper abdomen; its radiation was to the back and under the right shoulder-blade; its character was colicky and griping; its intensity was very great at times, but all attacks were not equally so; its duration was variable, usually about an hour or two. Attacks appeared to bear no relation to food; they might precede or follow a meal. During the attack she was nauseated but rarely vomited. With one attack, about two years before, distinct jaundice followed; and during one attack, while under observation in hospital at the time she came for diagnosis, her eyes showed decided yellowness of the conjunctivæ, the skin over the entire body became slightly yellow, her urine a dark brownish black, and her feces very light yellow. This patient was fat, of good color, and appeared well. No rigidity or tenderness could be elicited over the gall-bladder area. Her stomach showed no abnormality in size, position, or secretion. In fact, no evidence existed, except in the clinical history, that any serious pathological change had occurred in this patient's body. Yet at operation her gall-bladder was found small, shriveled, and shrunken, and contained two large stones, upon which it had contracted so that they completely filled it. Gall-bladder and stones were removed, and her pains never recurred.

So many of the cases of gall-stones present the same story over and over, with only minor variations, that it becomes monotonous to review their histories. It is interesting, however, to note the unusual variations from the ordinary, because these help us to recognize similar atypical cases another time; such is the following: A woman, aged forty-eight years, when seen first in June, 1913, had had "stomach trouble" for fifteen years past, worse for the past ten years. She had this trouble all the time, but also every month or two very violent attacks of pain, so severe as to require morphin. These started suddenly, and she felt as if in a vise, from the pain in front and back. At the outset she felt distended and full of gas. Then came the violent pain, steady, continuous; awful pressure with no intermittence, persisting until morphin was given. Attacks always began soon after a meal, and always seemed due to some food eaten, particularly to sour foods, as fruits and pickles. Between these attacks nearly all food distressed. Appetite was good, but she feared to eat. Distress came on an hour or two after eating; she filled up with gas and seemed much distended; and there was much belching. Such distress persisted for hours after food was taken. In the effort to get relief from these troubles she had been operated upon in September, 1912, for repair of lacerated perineum, suspension of a retroverted uterus, removal of both ovaries and tubes, release of intestinal adhesions, and removal of appendix. After this operation she was better for a time, but not for long. Therefore, in

February, 1913, another operation was done, for relaxation of vaginal walls and prolapsed uterus. But the following April she had another of her severe attacks of pain, and since then her stomach trouble had persisted constantly. This patient was obese and sallow. Her abdomen showed the characteristic rigidity and tenderness in the right hypochondrium, and her stomach a moderate hyperchlorhydria. In view of the history and findings a diagnosis was made of cholelithiasis, biliary colic, and reflex hyperchlorhydria.

Now comes the history that makes this case remarkable. Under routine medical treatment her attacks of pain disappeared and her stomach trouble ceased entirely for nearly three years. But, nevertheless, during these years she was never well. At one time she had a severe siege of "muscular rheumatism." She remained continually tired, exhausted, and anemic. In January, 1915, she had another attack of severe muscular pains in her chest wall. Later on she complained of constant aching and stiffness in her back and down both limbs, so severe as to prevent sleep. She had much headache, lost weight and strength, and in general felt wretched. Finally, after persistent suffering with pain in the back, headaches, and aching in the limbs, in April, 1916, her stomach trouble recurred and then she had a violent attack of her old pain. This led to immediate operation, and to the removal of one large gall-stone over three inches in circumference, another as large as a large acorn and about that shape, three others averaging an inch in circumference, and about 100 others, pea size or smaller, with very black, thick, infected bile. It seems clear that all the conditions arising during the three years' quiescence of the biliary colic were due to sepsis taking its origin from the gall-bladder, for all have entirely disappeared since the operation.

Finally is selected for review a case that calls attention to a complication of cholelithiasis, always present as a possibility, with every attack of biliary colic. A man, aged sixty-two years, seen in January, 1914, had been awakened at 2 A.M., on January 9, with intense pain in the pit of his stomach, radiating to his right side and through to his back. This lasted all day, like colic, and very severe; persisting also during the tenth day, with intermissions, but absent during the eleventh and twelfth days, only intense soreness remaining at the site of former pain. Early in the morning of January 13 he had another very severe attack, sudden in onset, at the right side of the abdomen, just at the edge of the ribs. On the afternoon of the ninth day he had a very severe chill, followed by fever and sweat; another such paroxysm at noon on the tenth day; a third on the eleventh day; a fourth during the forenoon on the twelfth day, with temperature rising to 105°; and a fifth late the same evening. Between these paroxysms the temperature became normal, falling with the profuse sweat. The patient was a very large, obese man, with slight icterus in conjunctivæ and skin. The abdomen showed ful-

ness and tenderness in the right costal groove, with moderate distention of the whole abdomen. Immediate operation advised revealed an acutely inflamed gall-bladder, containing purulent secretion, and 151 gall-stones, one of which had perforated the wall near the cystic duct and set up a localized peritonitis.

No reference has been made in the course of these case reports to *roentgen-ray examination of the gall-bladder*, because it is only very recently that improved technic has made it possible to obtain results in demonstrating the presence of gall-stones. At this time it is claimed that in about 50 per cent. of all cases, gall-stones will cast a shadow, so that it is undoubtedly in order to submit every suspected patient hereafter to an expert radiographer for his investigation. The writer has done this during the past year, but from the experience so far acquired the conviction is very strong that a negative roentgen-ray plate cannot be taken to exclude gall-stones, nor can a positive report always be accepted as conclusive; for in one recent instance in which the roentgen-ray plate showed shadows interpreted to mean gall-stones, no stones were found at operation.

As regards *stool examination for gall-stones* it is useless except soon after an attack of biliary colic, and very often negative then. The time so spent is not well repaid, because absence of gall-stones from the stool does not prove their absence from the gall-bladder; and the discovery of a gall-stone in the feces does not tell whether others remain in the gall-bladder or not. In the writer's experience, time is much better spent in sifting the history of these patients than in sifting their stools.

In considering the conditions that may be confused with gall-bladder disease and lead to error in diagnosis, *chronic appendicitis* stands out conspicuously above all others. Among the chronic cholecystitis diagnoses that came to operation, one proved to be chronic appendicitis; and among the cholelithiasis cases, three shared this fate. A description of these will show how difficult it is never to err. A woman, aged forty-four years, seen in March, 1912, stated that in the preceding August she had an illness characterized by slight pain in her right side and soreness just at the lower border of her ribs. Her skin became yellow and remained so for several weeks afterward. She had no fever at the time so far as she knew, but lost her appetite, and food distressed her. The whole attack lasted about two weeks. She had never been well since, gradually losing in weight and strength, and with constant stomach trouble—poor appetite, a sense of pressure and fulness after food; but no actual pain, no nausea or vomiting, no belching or waterbrash. She complained also of a sore spot and of darting pains in her right side, at the lower border of the ribs, present off and on for five years, but much worse and more constant since August. She had been a little jaundiced ever since her acute attack, sometimes more, sometimes less, but never so much since as at the outset. Under observation in

hospital she complained of pain in her right side, which she described as throbbing in character, a pressure, sense of tightness and clutching, severe enough to keep her awake at night; and in locating these sensations she pointed to the right side, at the lower border of the ribs, where she said she had, for months previous, a constant sense of soreness. She was obese; sallow but not jaundiced; with no mass palpable in the abdomen, but decided rigidity in the epigastrium and right hypochondrium, and with extreme tenderness on deep palpation, particularly over the gall-bladder area. The stomach was normal in size and position, but showed a definite hyperchlorhydria. The urine showed no bile and the feces no lack of it. At the operation advised for chronic cholecystitis, no evidence of disease was found in or about the gall-bladder, but a chronic appendicitis, with concretions within the lumen.

A man, aged fifty-one years, seen in March, 1913, complained of illness since the preceding October, characterized by loss of appetite, much gas formation and belching, frequent nausea, retching and vomiting after eating, and much pain in the right side, at the border of the ribs. This pain was constant for weeks at a time, but at times went away entirely. It was severe in intensity, but never like colic; it had been felt also in the back, on the right side. At the outset in October he had a chill, followed by fever, with terrific pain, requiring morphin repeatedly; this pain was located in the pit of the stomach at first, but later in the right side like the subsequent attacks. With the first attack he had no jaundice, but with a subsequent one in January his skin did become yellow for weeks. His abdomen showed rigidity and increased tension below the right costal margin and great tenderness on Murphy's maneuver, but no abnormality over stomach or appendix. The test-meal gave a normal secretion. Operation was advised for cholelithiasis. When it was performed the subsequent October no disease of gall-bladder was found, but a suppurative appendix, with a large abscess behind the cecum.

A woman, aged thirty-eight years, seen in May, 1913, very large and obese, gave a history of recurring attacks of abdominal pain, the first one seven years before, then about twice a year until the previous September, since then about every two months or six weeks. The attacks came with no warning at all, lasting until morphin was given, but never over a few hours. Her description of these attacks seemed typical of gall-stone colic. The pain was sudden in onset, like colic in character, as severe in intensity as when her baby was born; its site at onset was under the border of the ribs on the right side or in the pit of the stomach, radiating across to the left under the ribs and ultimately clear around into the back, so that it made a complete circle. Usually vomiting accompanied the attack, sometimes at the onset, sometimes after an hour, with repeated violent retching and straining, lasting even after the pain was gone. Attacks might occur in the early morning, rousing from sleep, or before

breakfast, often during the forenoon, never at night. Sour food would bring on an attack, as salad, pickles, or logan berries. She had never noticed any yellowness of the skin after an attack, nor any change in urine or feces. In the interval between she felt perfectly well; had an enormous appetite, ate very heartily, and it took a great deal of food to satisfy her. Her bowels were always constipated and never moved without aid. Physical examination was entirely negative, as regards stomach, gall-bladder, and appendix, and the abdomen seemed normal in every way. Suspecting gastric crises, careful investigation was made of all reflexes but no abnormality found. Stomach contents showed only a slight increase in acidity. Feces showed no ova of parasites. The Wassermann reaction was negative. The diagnosis made was cholelithiasis, with recurring attacks of biliary colic. At operation no disease of gall-bladder was found and no stones; no disease of stomach or duodenum, but the appendix was slightly enlarged, thickened, and clubbed. After removal it showed swelling of its mucous membrane, and its lumen filled with mucus. Smears of the latter showed many lymphocytes, a few polymorphonuclear leukocytes, a moderate number of short Gram-negative bacilli (probably colon bacilli), no other bacteria; sections showed some hyperplasia of lymph follicles, fibrous thickening of submucosa, areas of cellular infiltration, and some newly formed fibrous tissue in the subserosa. The pathological diagnosis was, therefore, chronic appendicitis. Clinical proof of its correctness was given by the fact that after the operation all attacks of pain ceased.

The last case of this sort presented itself in October, 1915. The woman, aged thirty-seven years, told the old familiar story of attacks of abdominal pain, recurring at intervals for fifteen years past, and gradually growing worse. At first these came about once a year, but they grew more and more frequent, until now they come as often as once a month. The pain appeared suddenly, with a feeling of bloating and distress in the pit of the stomach, gradually becoming very severe, and radiating to the right side and into the back. It was colicky in character and so intense as to require morphin for relief. Sometimes it lasted twenty-four hours, sometimes only two or three. She was always left very sore afterward, over the site of pain, as if someone had beaten her. She had never grown yellow with any attack, nor had her urine become dark or her feces light in color. At times she had chills and fever at the time of her attack, but only for a short time and not with all. She always vomited with any severe spell. Between times she had no digestive trouble, but was always constipated. This patient gave no signs of rigidity or tenderness or palpable mass over either gall-bladder or appendix. Her stomach contents showed a subacidity. Advised operation for gall-stones, she finally submitted to it in April, 1916. No disease of gall-bladder was found, but a chronic appendicitis; the

appendix was much enlarged and swollen and its lumen distended by pus.

How to avoid the error made in these cases is not altogether clear. Both conditions give rise to recurring attacks of abdominal pain. Ordinarily we depend upon the site of pain and tenderness, the radiation of pain, its character and intensity, to distinguish one from the other. But as shown by these histories, the clinical picture is not always definite. Either may give rise to chill and fever with leukocytosis, to jaundice, and to vomiting as coincident manifestations; and while appendicitis may have pain referred to the right costal margin and back, gall-stone colic may exceptionally cause pain referred down into the right side of the abdomen. It seems inevitable, therefore, that occasionally one will be mistaken for the other, in spite of every care.

Other conditions that must be distinguished from biliary colic are gastric and duodenal ulcer, gastric crises of tabes and renal colic. As regards ulcer, the error is conceivable; but the characteristic history of chronic gastric ulcer, the findings by physical examination, stomach analysis, and roentgen-ray plates should serve at least to exclude cholelithiasis, even though other possibilities for error remain. Examination of the reflexes, and Wassermann reaction, with lumbar puncture in any dubious case, should remove all doubt as to gastric crises. Renal colic has such a very different history as regards urinary symptoms and signs, and investigation is now so definite in its results by cystoscopy, ureteral catheterization, pyelography, and roentgen-ray plates, that one can rarely fail to recognize the underlying kidney disease if the colic attacks are renal in origin.

III. Cancer of the Gall-bladder. Two cases of this were met with in the series, one discovered as a result of operation and the other diagnosed before operation. The first case was a woman, aged fifty-two years, who had the usual typical cholelithiasis history, of recurring attacks of pain in the upper abdomen, for ten years previous, absolutely characteristic of biliary colic, except that she had never had jaundice with any attack, nor fever. The right costal groove was more full than the left, more rigid and very tender, but there was no palpable mass. Stomach analysis showed a decided hyperchlorhydria. At operation, advised for gall-stones, there were found many adhesions around the gall-bladder and great thickening and hardness of its walls, suggesting malignancy; with about thirty stones of various sizes and shapes. The stones were removed and the gall-bladder excised. The pathologist reported later on that sections from the gall-bladder showed carcinoma.

Such a sequel of chronic irritation by gall-stones is not surprising, and it is remarkable that it does not more often occur. The clinical history and the findings by physical examination were all those of cholelithiasis and biliary colic, and no other clinical diagnosis could be made. The pathological examination of removed tissue was what

showed the real condition, not suspected previous to operation. However, in the other case of cancer of the gall-bladder met with in this series the diagnosis could be made clinically. The patient was a woman, aged sixty years, seen in May, 1914. She complained of a lump in her right side, discovered about four weeks before. Her past history gave no evidence of attacks of biliary colic or of any chronic indigestion. She began to suffer with pain in her back several months before, but the lump in her side was only recently found. There had been some pain in this region but no severe suffering. There had been no distress from food and no vomiting. She had grown very yellow, however, for two weeks previous, and had lost much weight. The patient was moderately jaundiced. In her abdomen was found a hard, smooth, tongue-like tumor, projecting from beneath the costal margin in the region of the gall-bladder, half-way to the navel. This was freely movable, not tender, not nodular, and could be grasped and moved from side to side. The liver was not increased in area; its lower border, palpable on deep breath, was not nodular or tender; and was found just beneath the costal margin, while the rounded tumor extended as low as the navel when the patient took a deep breath. On inflation of the stomach its greater curvature was found 10 cm. below the navel; no peristaltic wave was elicited or other evidence of pyloric obstruction; and the tumor was found to be distinctly to the right of the inflated stomach outline. Stomach contents showed a complete absence of free HCl and a total acidity of 6. The feces were clay color, putty-like in consistence, and showed an excess of fat. The urine was dark brown and showed bile. The Wassermann reaction was negative. Exploratory operation showed carcinoma of the gall-bladder and ducts, with metastatic nodules in the liver. The tumor felt was the enlarged gall-bladder, corroborating the impression given by clinical examination.

In conclusion, the most valuable lesson to be drawn from these case histories and from the experience acquired in obtaining them and the others in the group to which they belong is that the older methods of diagnosis are still the ones upon which we must rely. Painstaking efforts in eliciting an orderly and complete history not only of the patient's complaint but of all other incidents in the previous health; careful and intelligent use of the eyes, the finger tips, and the ears in acquiring information about the patient; and good judgment in sifting and interpreting the facts so obtained are still the methods that surpass all others in diagnosis. The newer laboratory and roentgen-ray aids are exceedingly valuable and never to be overlooked, but not to be relied upon as short-cuts and labor-saving devices to supersede the other means described, as seems to be too much the tendency in this day.

MEDICAL ASPECTS AND DIAGNOSIS OF DISEASES OF THE GALL-BLADDER.[1]

By David Riesman, M.D.,
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The diseases of the gall-bladder in which we are most interested are cholecystitis and cholelithiasis. As an independent affection, inflammation of the gall-bladder is not common. In the majority of cases the gall-bladder is the seat of stones. Nevertheless, we must take cognizance of non-calculous inflammation. It is met with in typhoid fever, pneumonia, food-poisoning, etc., and manifests itself by tenderness in the gall-bladder area, by leukocytosis, and usually by jaundice. But even in apparently primary cases an unsuspected gall-stone may exist, as I once observed in a case of typhoid fever. As non-calculous cholecystitis, whether due to the typhoid bacillus or other causes, may closely resemble gall-stone colic, some physicians and surgeons, to avoid embarrassing explanations to the laity, no longer make a diagnosis of gall-stones, but merely of gall-bladder trouble. Surely it is an uncomfortable feeling not to find at operation the gall-stones one has predicted. In such an impasse one thinks of the practice of Conan Doyle's Dr. Winter, who carried stones in his pocket to meet these emergencies. Acute cholecystitis, especially the calculous form, is often of a fulminant character, producing all the signs of a severe septic infection with localized peritonitis. In one case, seen several years ago, in which the gall-bladder was filled with stones and pus, the onset was so acute as to suggest perforation of a gastric ulcer. In the diagnosis of such cases the history is of great moment; the patient generally has had attacks of pain in the upper abdomen and has suffered from indigestion and possibly jaundice. If the patient is a stout woman past thirty, the suspicion of gall-bladder infection is strengthened. On physical examination the gall-bladder in these cases can sometimes be felt, especially if a rolled-up blanket or pillow is placed under the back and the abdomen is palpated very lightly with the warmed hand. A large gall-bladder generally means a stone in the cystic duct. In such cases the liver often projects a considerable distance below the costal arch in the form of the so-called Riedel's lobe. Cholecystitis sometimes occurs in women of advanced years who never have had any gall-bladder trouble before. As I have seen it the attack has always followed a gross indiscretion in diet, and during the first day or two has resembled "ptomain poisoning." The symptoms are sudden epigastric pain with nausea and vomiting, prostration, and moderate fever. On the

[1] Read as part of a symposium at a meeting of the American Gastro-enterological Association, Washington, May 8, 1916.

second or perhaps the third day an enlargement in the liver region with great tenderness on pressure can be made out. This enlargement is evidently the swollen gall-bladder. A slight leukocytosis and congestion over the base of the lungs complete the clinical picture. Jaundice has not occurred in my cases.

I shall not dwell on the well-known symptoms of gall-stone colic except to say that the pain is much more often in the epigastrium than the text-books state. It may travel to the back, to the right side or to the left, and to either or neither shoulder. Nausea and vomiting while common are not rarely absent. A chill is of significance. Most patients complain of a sense of upward pressure during an attack of gall-stone colic. If a patient states that in one or more attacks the pain was so severe as to require a morphin injection, I take that as contributory evidence of biliary colic. Jaundice is not common; its presence is of great diagnostic value, its absence without significance. If every patient's urine is examined within forty-eight or seventy-two hours after an attack, traces of bile will not rarely be found. Many patients who declared that they never were jaundiced told me on inquiry that after an attack of pain they had passed very dark urine.

The pain in gall-stone colic may be left-sided. In a patient whom I saw several years ago with Dr. Farr the pain was never anywhere except in the left hypochondrium. Operation revealed a single large stone in the gall-bladder, with adhesions between the latter and the stomach.

An attack of pain in the upper abdomen which under other circumstances I would attribute to gall-stones, I should feel quite sure *was* due to that cause if the patient was a pregnant or puerperal woman. This is due to the fact that, as I have often observed, the first attack of biliary colic not rarely occurs during or soon after pregnancy.

It is always well in cases of upper abdominal pain of obscure origin to have the bowel movements searched for gall-stones. They are not infrequently found.

Pancreatic stones may cause symptoms similar to gall-stones. They are so rare that little need be said about them. It has been stated that the Roentgen ray shows pancreatic calculi more clearly than it does gall-stones.

Gall-stone disease may be simulated by floating kidney even to the point of jaundice. The discovery of a loose kidney and a history that the pain is relieved by lying down, and that the attack subsides with the passage of a large amount of pale urine would make us think that the attack was a so-called Dietl's crisis and not biliary colic.

In several instances I have been much perturbed by a difficulty in deciding between appendicitis and gall-stone. If the patient is young, thin, and spare, and has a history of some intestinal dis-

turbance, either diarrhea or constipation, at the time of the attacks, I should consider these facts suggestive of appendicitis rather than of gall-stones, even if the pain were near the costal border. Perhaps the sign pointed out by Dr. Aaron will prove helpful.

Surgeons are prone to draw very sharp distinctions between gall-bladder disease and gastric ulcer, no doubt because many of the cases they see group themselves readily under one or the other heading; but a physician seeing ambulatory cases in his office and in dispensary practice often has great difficulty in deciding whether a patient has gall-stone disease or gastric or duodenal ulcer. Many who complain of definite symptoms that seem to point to one or the other have neither, and are examples of so-called functional disturbance. I have seen several such patients in whom operation showed nothing to account for their symptoms.

The most difficult cases are undoubtedly those in which the gall-bladder is adherent to the stomach or the bowel, either as the result of primary disease of these parts—generally ulcer—or of repeated attacks of cholecystitis. We have, then, a fusion of hepatic and gastric symptoms, often with hyperchlorhydria, and it requires long and patient study to determine which is the underlying disease. A duodenal ulcer adherent to the fundus of the gall-bladder may produce symptoms scarcely distinguishable from gall-stone colic. In the diagnosis three things are necessary: A careful history, a roentgenologic study by an expert, and a physical examination, with all the modern laboratory investigations, including the use of the duodenal tube of Einhorn. Each of these methods may be counted upon to give about 30 per cent. of evidence. In cholelithiasis the Roentgen ray proves reliable, *i. e.*, shows the stone, in about 50 per cent. of the cases; it gives far better results in gastric and duodenal ulcer.

One of my patients, a physician, had symptoms of cholecystitis with tenderness in the gall-bladder area. The pains were so severe that he had taken to inhaling ethyl chlorid, and was using the drug in large quantities, $20 worth in a week. Operation showed a duodenal ulcer about to perforate, with the gall-bladder adherent to the base of the ulcer. In the patient's history the symptoms of duodenal ulcer seemed to be almost completely overshadowed by the secondary trouble in the gall-bladder.

One point of importance that has impressed me as of possible value in these cases is the persistence of the pain. Attacks of pain only of gall-bladder origin rarely last longer than a few hours or a day or two, while those of ulcer frequently last much longer. Gall-bladder attacks are more often nocturnal than those due to gastric ulcer, and are less related to the food intake. It is true, duodenal ulcer usually causes pain at night, but the pain is relieved by food, drink, or alkalies, and is much more regular in appearance, the patient being wakened from sleep almost at the same hour every

night. Many patients suffer from gall-stone colic whether they diet or not.

Sometimes cholangitis closely simulates gall-stone disease. In addition to pain there may be intermittent fever, with or without jaundice. Such cases are most perplexing. Sometimes there is nothing but an intermittent fever (Charcot's intermittent fever), which may extend over a period of weeks and even months. Jaundice may or may not be present. In one very protracted case that came under my observation, jaundice never occurred. Although gall-stone is the most natural diagnosis, the operation may reveal nothing but a gall-bladder filled with dark, thick, infected bile. Standing at the operating table one is inclined to think that the findings are insufficient to explain the clinical symptoms, and yet drainage of the biliary passages is all that is necessary to bring about a cure.

Gall-stone colic may be closely simulated by the crises of locomotor ataxia, the pains of which are often so severe as to require morphin injections. I believe it is a good rule in all cases of supposed gall-stone colic to test the knee-jerk, the station, and the pupils. As regards the last, it should be remembered that one might think an Argyle-Robertson pupil existed, when in reality the myosis was due to morphin. As a rule the gastric crises attacks are irregular in occurrence and extend over a long period (from several days to two weeks), and are not noticeably influenced by drugs, even by morphin. The Wassermann test is of value.

Pleurisy and pneumonia may counterfeit the picture of gall-bladder disease in a well nigh perfect manner. I recall the case of a patient who had been seized with pain in the right upper abdomen, jaundice following a day or two later. The attending physician had diagnosed gall-stone colic, but a careful examination disclosed lobar pneumonia.

Sometimes a sharp pain in the *back* or in the right chest *posteriorly* is a manifestation of gall-stone disease. I have seen several instances. The diagnosis is extremely difficult; one must be governed by the absence of renal symptoms, and perhaps by finding, notwithstanding that the pain is in the back, tenderness in the gall-bladder area.

Cases are common in which the symptoms are those of nervous dyspepsia. The patients never have severe pain, but suffer for years from "gas," belching, bloating, indigestion, and various neurasthenic manifestations. The fact that neither diet nor the rest cure to which many are subjected is of any permanent value should arouse the suspicion of organic disease, which might be ulcer, appendicitis, or gall-stones. To differentiate properly among these possibilities, especially between ulcer and gall-stone, is impossible by any rule of thumb. The clinician must in the last analysis be guided by his sixth sense, clinical intuition.

That there should at times be difficulty in distinguishing between

gall-stone disease and angina pectoris might seem incredible, yet it is true. Only a careful analysis of the history and a thorough physical examination will prevent mistakes. Apart from this indirect relation between gall-stones and angina pectoris, due to a remote similarity in symptoms, there are also more direct relations existing between the gall-bladder and the heart. The facts, as I have observed them, are about as follows: In a certain number of patients who have suffered from gall-bladder infection, often unknown to themselves, cardiac symptoms appear. These vary in character. Quite frequently a systolic mitral murmur is found, usually without any signs of cardiac failure. In other cases, in which the myocardium is evidently affected, the symptoms are those of sudden acute heart attacks characterized by dyspnea and cyanosis; in still others the attacks are as far as one can tell anginal in character. Now it is a curious fact that in nearly every case, at least in my experience, the heart symptoms have disappeared after operation. The importance of this phase of the subject is that one may consider the case one of a hopeless heart affection and overlook the causative factor, removal of which would cure the cardiac condition. On the other hand many a physician is deterred from advising operation on finding some cardiac disturbance or a heart murmur, because he looks upon it as a contra-indication to operation. In reality it is to be looked upon, unless too far advanced or clearly due to an independent disease, as a distinct indication for operation.

Lately attention has been called to a possible relation between infections of the gall-bladder and disease of the joints. Granted that multiple arthritis is in many instances a secondary process, there is no reason why the gall-bladder may not be the primary focus as well as the gums or the tonsils. In one case of arthritis deformans, in which a gall-bladder packed with stones was removed by Dr. Deaver, the joint condition was in nowise influenced. As the patient had had, however, the trouble for years, little was to be expected.

Much difficulty is presented by certain cases of chronic obstructive jaundice. While in middle-aged and elderly persons chronic jaundice is always suggestive of malignant disease, especially of the pancreas, it is possible to have such jaundice as the result of adhesions, stone, or chronic pancreatitis. I have sometimes thought that early itching was more common in malignant disease. If the gall-bladder is palpable the chances are against stone and in favor of external obstruction. Jaundice varying in intensity is nearly always due to stone in the common duct. There may not be in such cases any history of pain or at least any history of sharp colic. A patient with chronic jaundice may lose a great deal of flesh without having carcinoma. The significance of these facts is their bearing on treatment, a discussion of which is beyond the scope of this paper.

GALL-BLADDER DISEASE: A PROGRESSIVE INFLAMMATION: ITS TREATMENT, CHOLECYSTECTOMY.[1]

By Russell S. Fowler, M.D., F.A.C.S.,

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The title of this paper explains its purpose. The author believes: (1) that gall-bladder disease is a progressive inflammation from its incipiency; (2) that its treatment is early cholecystectomy before the disease has advanced beyond the gall-bladder. In furtherance of this purpose the subject has been treated in as simple a manner as possible, and it is hoped that with the aid of the illustrations its object will be accomplished.

The material for this study consists in upward of 100 gall-bladders presenting all degrees of pathological changes removed by the writer during the last ten months at the German Hospital and the Methodist Episcopal Hospital. For assitance in the miscroscopic study of the sections acknowledgement is extended to Doctors T. H. Dexter and W. W. Laing.

The inflammatory lesions of the gall-bladder so merge one into the other that it is impossible to secure specimens that are typical of one stage of the inflammatory process alone. So true is this, indeed, that it is quite logical to conclude that all are but different stages in a progressive inflammation. This progressive inflammation may be divided into three stages:

1. *Cholecystitis catarrhalis subacuta*, a first stage, where macroscopically the mucous membrane is but slightly affected and the rest of the wall not at all, but which presents microscopically characteristic changes. Grossly, the gall-bladder appears normal except for a more than usual velvety appearance of the mucous membrane. Stones may be present or absent. If present they are usually small. The aspirated bile is thicker than normal and more viscid. Microscopically (Figs. 1, 7, 8), the villi are broadened, elevated, and infiltrated with lymphocytes. This infiltration may extend into the wall of the gall-bladder. This stage I have described elsewhere as cholecystitis catarrhalis subacuta, with the added observation concerning the hypertrophied musculature, which latter seems to me to be of importance in placing this pathological picture in its true place as the earliest inflammatory stage in the progressive inflammation affecting the gall-bladder; for if the increased viscidity of the bile is due to increased activity of the mucous glands and partial though slight obstruction to drainage, then the hyper-

[1] Read before the Brooklyn Pathological Society, October 12, 1916.

trophy of the gall-bladder musculature naturally fits in the picture. Stronger efforts at expulsion are needed to empty the viscus, and until the musculature is invaded by the progressive inflammation, and finally impaired, the increased burden that is put upon it results in hypertrophy.

In addition, Luschka's spaces are somewhat dilated. In those cases in which no stones are found it is possible that they may have passed through the ducts. It is also just as probable that this is a pre-gall-stone stage.

FIG. 1.—Cholecystitis catarrhalis subacuta, showing a broadened villus elevated and infiltrated with lymphocytes. At the base the infiltration extends into the gall-bladder wall. The musculature shows hypertrophy. There is a somewhat dilated Luschka's space.

2. *Cholecystitis Catarrhalis Chronica.* Gross: Externally the gall-bladder does not present evidence of inflammatory change except for the gland at the cystic duct, which is usually enlarged. Stones may or may not be present. Here and there in the mucous membrane are minute yellow bile-stained areas of destroyed epithelium. These may be scanty or numerous. When plentiful they give a speckled appearance to the gall-bladder mucous membrane. Other areas show the characteristics of cholecystitis catarrhalis subacuta or appear normal, or the site of slight acute inflammation.

Microscopic (Figs. 2 and 3): The mucous membrane villi are thickened, the apices in places denuded of epithelium. It is these denuded areas which appear macroscopically as yellow specks.

This is the characteristic lesion. There is infiltration by lymphocytes of the mucous membrane and submucous tissues, and here

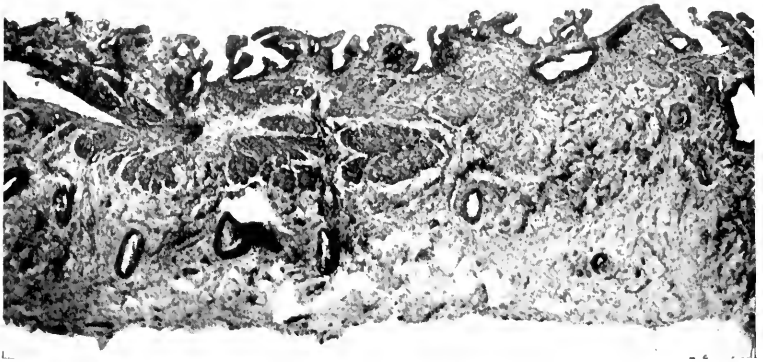

FIG. 2.—Cholecystitis catarrhalis chronica. The bases of the villi are broadened, the apices in places denuded. Lymphocytic infiltration of the mucous membrane and submucous tissues, and here and there of the hypertrophied musculature (beginning cholecystitis chronica). (Low power.)

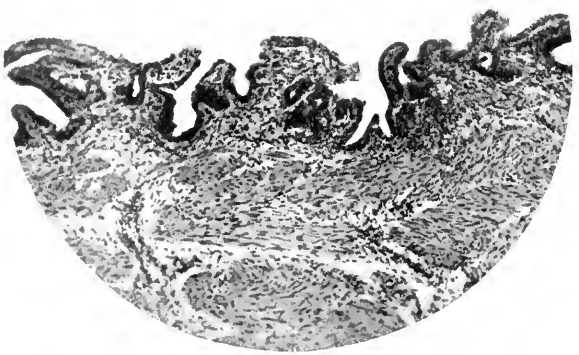

FIG. 3.—Cholecystitis catarrhalis chronica, showing in detail the changes in Fig. 2. (High power.)

and there of the hypertrophied musculature (beginning cholecystitis chronica). Luschka's spaces are somewhat dilated.

Rarely is a specimen of cholecystitis catarrhalis chronica found which does not show characteristics in various parts of the specimen

FIG. 4.—Cholecystitis chronica. Lymphocytic infiltration into all parts of the gall-bladder wall. The musculature is markedly invaded. A villus stump is shown. (High power.)

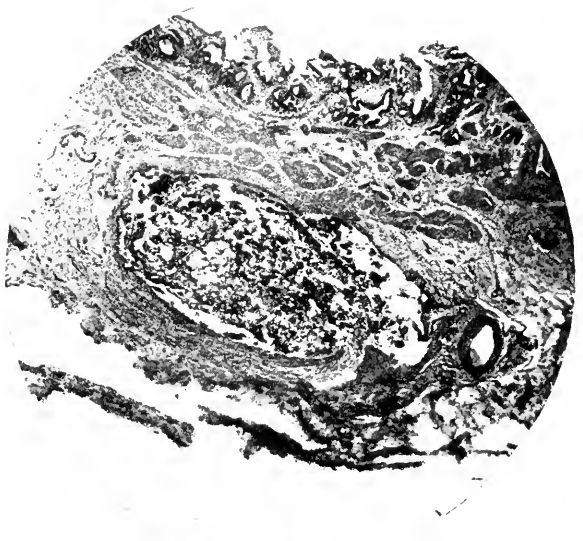

FIG. 5.—Cholecystitis chronica with stone formation in a Luschka space.

of the three stages of the progressive inflammation characteristic of gall-bladder disease—cholecystitis catarrhalis subacuta, cholecystitis catarrhalis chronica, and cholecystitis chronica. The distinction between the three is made on the predominance of the lesion appertaining to each. It is common, however, to find cholecystitis chronica without the first two stages.

FIG. 6.—Cholecystitis catarrhalis acuta. Though the papillæ including the tips are well covered with epithelium, the mucous membrane shows the following deviation from the normal: The cell outlines are for the most part obscured by cloudy swelling, though the nuclei are fairly distinct. There is a slight tendency to leukocytic infiltration in some areas, especially beneath the epithelium. A mild but distinct attempt at papillomatous formation is shown in the right half of the section. The muscle shows little if any change. Under the high power the infiltration beneath the epithelium is shown conclusively and there is also shown occasional and mild engorgement of some of the blood spaces in the papillæ, and the lymphoid areas are enlarged and engorged. The acute catarrhal differs from the subacute in the more marked changes in the mucous membrane which is hypertrophied and cloudy. The infiltration of the mucous membrane is intense.

3. *Cholecystitis Chronica.* Gross: Unmistakable evidence of chronic inflammation.

Microscopic (Figs. 4, 5, 9, 10): The entire gall-bladder wall is affected. The mucous membrane is lacking for the most part, being replaced by scar tissue; stumps of scar tissue represent what is left of the villi. There is infiltration of lymphocytes into all parts of the gall-bladder wall. The musculature is markedly invaded and more or less transformed into fibrous tissue. Here and there are areas of contraction where the process has been longest producing

macroscopically irregularities of the surface. It is logically what might be expected of a continuance of cholecystitis catarrhalis chronica. All stages of both the previous processes may be present, but mostly the picture is of chronic inflammation, with only an occasional area of mucous membrane.

The characteristics of this chronic inflammation are modified by pressure caused by chronic obstruction of the cystic duct. This occurs sufficiently often to be dignified by a separate subtitle, cholecystitis chronica cystica. Gross: such gall-bladders (hydrops) present unmistakable evidence of chronic inflammation, are

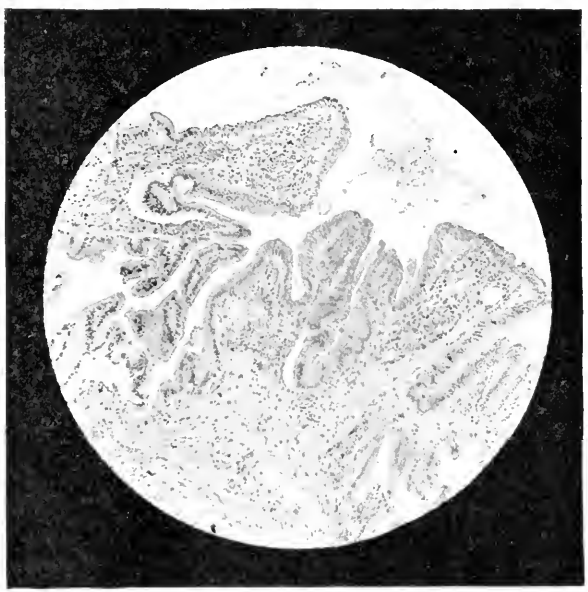

FIG. 7.—Cholecystitis acuta superimposed on cholecystitis catarrhalis subacuta. The bloodvessels of the muscular coat show an engorgement similar to that noted in the mucous membrane, and there is a distinct diffuse round-cell infiltration. (Low power.)

increased in size, sometimes enormously so, pale in color, the mucous membrane for the most part lacking, contents limpid fluid; wall thinned from pressure; obstruction usually by stone in the neck of the gall-bladder or in the cystic duct.

Microscopic: There is little if any mucous membrane present; what is found is flattened from pressure; the wall is formed of elastic connective tissue, with here and there muscle nuclei, and if the process is not too old, some muscle tissue.

These three stages—cholecystitis catarrhalis subacuta, cholecystitis catarrhalis chronica and cholecystitis chronica—form the large proportion of cases of gall-bladder disease. They are all

stages of the same inflammatory process, and are progressive. On them may be grafted other varieties of inflammation and carcinoma. Of the other varieties of inflammation we have:

Cholecystitis catarrhalis acuta (Fig. 6).
Cholecystitis acuta (Figs. 7 and 8).
Cholecystitis phlegmonosa acuta (Fig. 9).
Cholecystitis hemorrhagica acuta (Fig. 10).

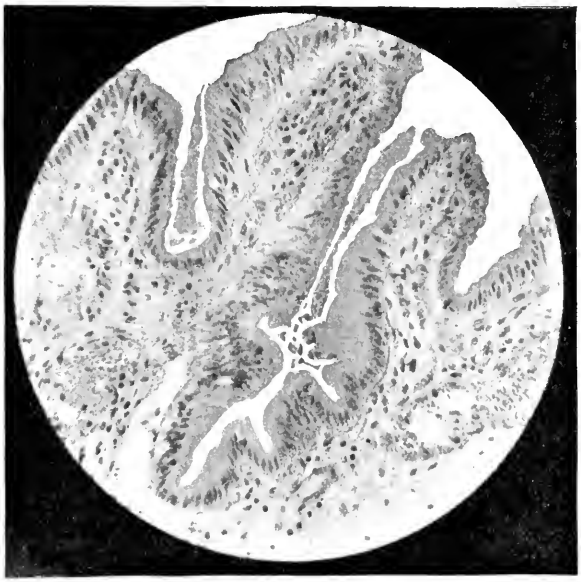

FIG. 8.—Cholecystitis acuta superimposed on cholecystitis catarrhalis subacuta. The villi are moderately but distinctly thickened. The bloodvessels of the mucous membrane are distended, and the villi show distinct leukocytic infiltration and some hemorrhagic extravasation. The epithelium of the villi including that of their tips shows distinct excessive proliferation. The lumen of the gall-bladder especially between the villi shows accumulation of mucus, leukocytes, red blood cells and detritus. (High power.)

Of these, the first may be present with but slight evidence of cholecystitis catarrhalis subacuta and no evidence of the other progressive inflammatory changes. Whether it precedes the subacute stage is, in my opinion, questionable. I believe that the sequence of events is: (1) cholecystitis catarrhalis subacuta (induced by interference with drainage and very mild infection); (2) cholecystitis catarrhalis chronica, the logical sequence of a continuation of the subacute stage; (3) cholecystitis chronica, the extension of the progressive inflammation already existent to other parts of the gall-bladder wall, together with a more pronounced inflammation and destruction of the parts previously involved in the subacute catarrhal and chronic catarrhal stages.

Of the remaining three—cholecystitis acuta, cholecystitis phlegmonosa acuta, and cholecystitis hemorrhagica acuta—none is ever present without evidence of cholecystitis catarrhalis chronica or acuta or cholecystitis chronica. An acute ulcerative process (cholecystitis acuta ulcerativa) may supervene on either.

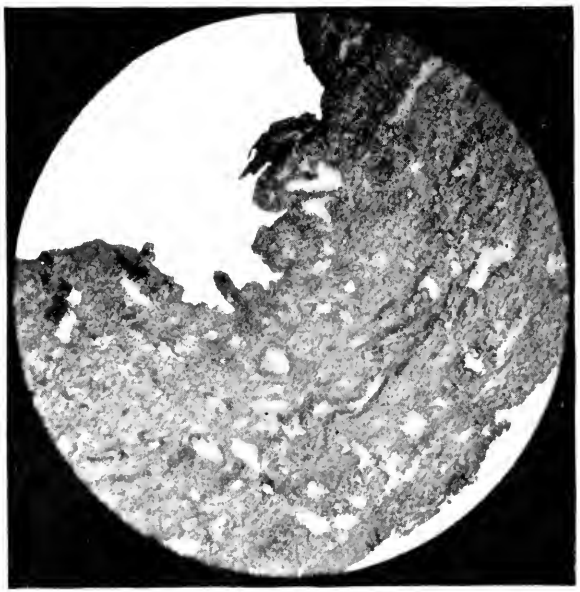

Fig. 9.—Cholecystitis phlegmonosa acuta superimposed on cholecystitis chronica. This section shows an ulcer beginning in the mucosa and involving the gall-bladder wall. The mucous membrane is absent and at the area where it should exist there is a depression the surface of which is covered with leukocytes, red cells and detritus. The depression that represents the ulcer invades the muscular coat to a considerable depth. The muscular coat itself shows marked round-cell infiltration diminishing in direct proportion to the distance from the ulcerative surface. There is marked hyperplasia of connective tissue at the expense of the muscle bundles which are distinctly thinned out and separated by hyperplastic connective tissue. The entire gall-bladder wall is involved in an acute phlegmonous process superimposed on chronic cholecystitis, the existence of chronic cholecystitis being shown by the scanty muscle bundles with interposed connective tissue.

A chronic ulcerative process (cholecystitis chronica ulcerativa) may supervene from general pressure in hydrops or local pressure from stone in cholecystitis chronica.

Cholecystitis catarrhalis papillomatosa may be associated with cholecystitis catarrhalis acuta (Fig. 6) or cholecystitis catarrhalis chronica (Figs. 11 and 12). The author has found it once in both conditions. There is no reason why it should not be present in an otherwise normal gall-bladder or why a gall-bladder the seat of a papilloma should not also be subject to any other lesion.

Carcinoma is found engrafted on cholecystitis chronica (Fig. 13) and as cholecystitis papillomatosa malignum (MacCarthy) and cholecystitis catarrhalis carcinomatosa (MacCarthy).

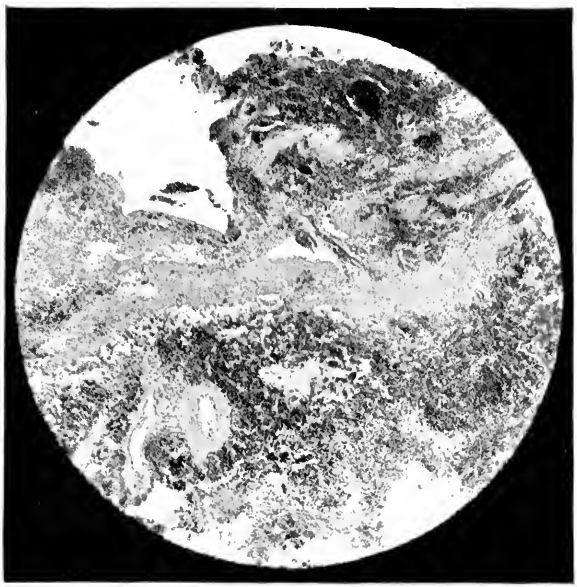

FIG. 10.—Cholecystitis hemorrhagica acuta superimposed on cholecystitis chronica. The mucous membrane is destroyed. The cells of the muscular coat show various stages of cloudy swelling and coagulation necrosis. Their protoplasm has a homogeneous appearance, their nuclei are indistinct and cell outlines are blurred or absent. Bloodvessels are distended with red cells and the tissue generally shows a marked extravasation of red cells and a diffuse leukocytic infiltration of the muscular wall, irregular in distribution, and with some tendency to localization in minute areas the prototype of microscopic abscess foci. If this section were considered by itself, the picture would be one of acute hemorrhagic cholecystitis, for the cloudy swelling of the muscle layers does not show any evidence of chronic inflammation, but section of other parts of the gall-bladder shows indubitable evidence of chronic cholecystitis. In some areas the mucous membrane shows coagulation necrosis of the single layer of columnar cells covering the papillæ. The cells appear granular, vacuolated and have lost definite outline, though the nuclei remain clear and sharply defined. In the papillæ and beneath these cells the papillæ show a marked hemorrhagic and leukocytic infiltration which involves also, to a less extent and in an irregular way, the muscular coat. Here also appears some connective-tissue hyperplasia indicating a chronic factor in the process. The tips of the papillæ are not denuded.

CONCLUSIONS. From a consideration of all of the above it is logical to assume that cholecystectomy is indicated in all diseases of the gall-bladder whether causing mild or severe symptoms. The operation is not done for the purpose of removing stones, for these may or may not be present, but for the purpose of removing tissue diseased as a result of a progressive inflammation. Just as soon as this inflammation has reached a point where the efficiency of the

gall-bladder is impaired and symptoms result, just so soon should the gall-bladder be removed.

Whether gall-stones are present or not is immaterial, for they are but one of the ways in which an already existent inflammation expresses itself. Personally, I do not believe there is any such thing as innocent gall-stones, but that they are the product of inflammation; that a gall-bladder once infected is always infected, and such a gall may become at any time a source of real danger to the patient through either acute exacerbation of the inflammation or through change to carcinoma during middle or later life.

FIG. 11.—Cholecystitis catarrhalis papillomatosa associated with cholecystitis catarrhalis chronica. (Gross specimen.)

Whenever possible, cholecystectomy should be performed early, not only for the reasons stated, but also because inflammations of the gall-bladder are, for the most part, probably always, recurrent and progressive, and if the inflammation is allowed to follow its natural trend at the very least there results adhesions, which in their turn produce annoying and in many instances disabling symptoms. So many operations have been performed on the terminal pathology of this condition, with an attendant high mortality and disability from already existing complications, that it is time for early operation to be advocated, because early operation at a time when the disease is limited to the gall-bladder means, at the very least, the

saving of much discomfort and inefficiency later in life. At all events the patient should be given an opportunity to choose in the early stage of the disease whether he wishes to continue to be subject to recurring attacks of so-called indigestion, with the added dangers of acute inflammation, and the final danger of carcinomatous change.

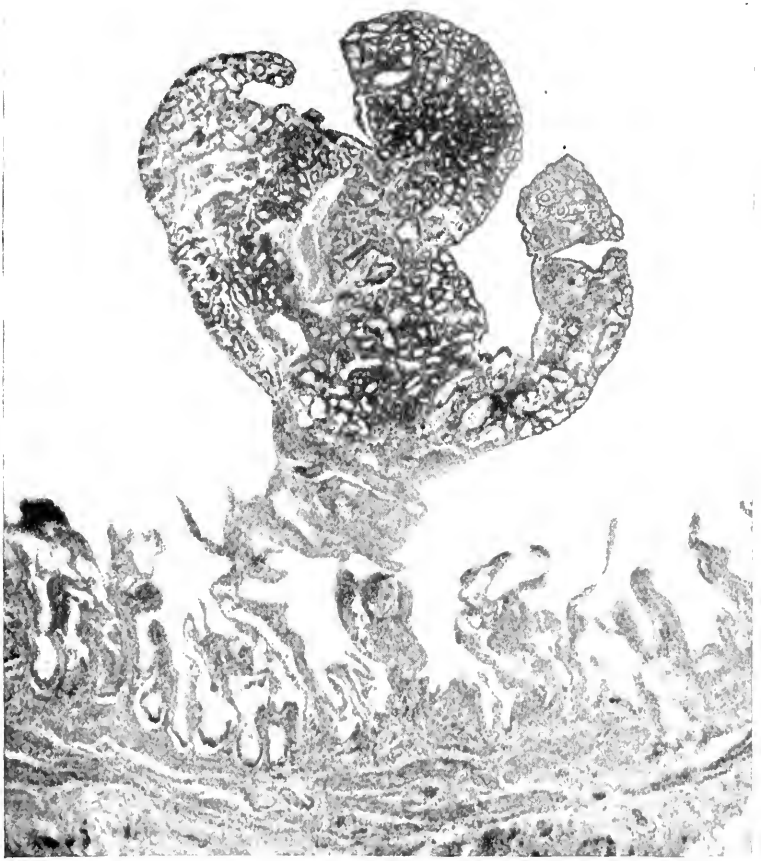

FIG. 12.—Cholecystitis catarrhalis papillomatosa associated with cholecystitis catarrhalis chronica. Note the slender base of the papilloma. (Low power.)

Formerly the high mortality of operations in this region was thought to be a bar to operative interference except in advanced cases; it is these very cases which are responsible for the high mortality; the disease should not be allowed to progress to this point. The lesion is initiated in the gall-bladder, and early removal of the gall-bladder will prevent the complications above stated,

and also will be attended with an extremely low mortality. This mortality should be no higher than that attendant upon operations for chronic appendicitis. Personally, I have never had a death from an operation upon the gall-bladder in which the disease was limited

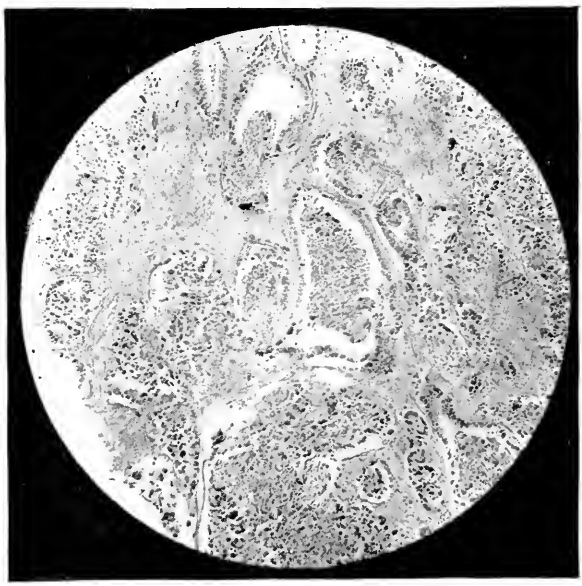

FIG. 13.—Carcinoma superimposed on cholecystitis chronica. The portion of the gall-bladder from which this section is taken is very thick and dense. The section shows a great preponderance of dense fibrous tissue in which is a glandular or adenomatous type of carcinoma. There are also many areas of carcinoma cells infiltrating the fibrous tissue in a lawless way. These cells differ morphologically from those of simple hyperplasia in that the nuclei are large, irregular in shape and size, and have irregularly distributed chromatin. In contrast to this are found occasional normal glandular elements consisting of a tubular arrangement of a single layer of columnar or cuboidal cells, on a basement-membrane and presenting no deviation from the normal uniformity of size, shape and pigmentation of cells and nuclei.

to the gall-bladder itself. The cases in my experience which have succumbed have been those in which carcinoma was present or in which the disease had extended to the common and hepatic ducts, or in which there was gangreous inflammation and perforation.

PERICARDIOTOMY FOR SUPPURATIVE PERICARDITIS FOLLOWING PNEUMONIA.

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Operative intervention in wounds of the heart and pericardium has become so successful in recent years that it is reasonable to hope that surgery may be employed more frequently and more successfully in non-traumatic suppurative pericarditis. In order to stimulate discussion on this topic we present this report.

In a series of papers by American writers, Roberts,[1] 1897, Porter[2], 1900, Eliot,[3] 1909, and Rhodes,[4] 1915, there has appeared an exhaustive presentation of the subject of suppurative pericarditis, with a collection of the reported cases of pericardiotomy for suppurative pericarditis. "The cases numbered 86, of which 45 recovered and 41 died, a percentage of 52.3 recoveries against 47.7 deaths. In the complete series the infecting organism is reported in but 21, the pneumococcus was found in 9 cases, staphylococci in 4, streptococci in 2, the colon bacillus in 1, the Bacillus pyocyaneus in 1, and a 'double coccus' in 1." (Rhodes.)

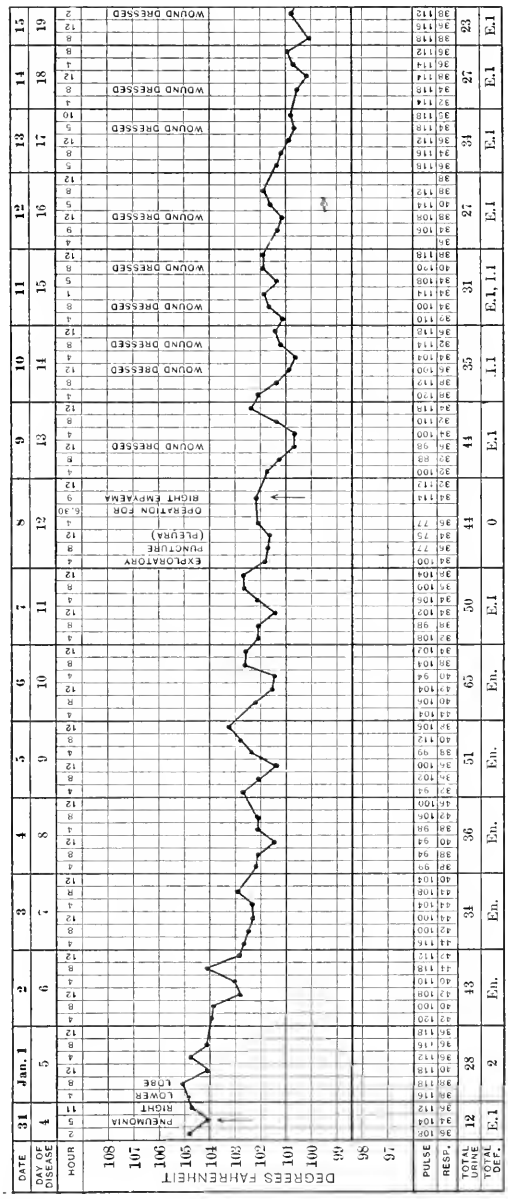
In connection with the case here presented, a case of pericardiotomy for suppurative pericarditis following pneumonia and empyema, we present synopses of the reports of similar cases. We also revised the detail of the technic of paracentesis pericardii and pericardiotomy.

Case Report.—Patient male; aged forty-seven years; occupation, engineer. Family and past history negative. Patient has been under the care of one of us (Camac) for various illnesses for the last fifteen years. These illnesses had no bearing upon the present attack. On December 24, 1915, at the office of one of us (Camac) patient was seen for a furuncle on the back of the neck, which was opened and dressed. On December 29, the wound was practically healed.

On December 30 the patient was seen at his house, and complained of a slight pain in the lower right axilla, on taking a deep breath. Examination showed a few very fine, almost inaudible crepitant rales at the right base, with somewhat harsh, vesicular breathing. Temperature, 104°. He was flushed and felt ill. Respirations,

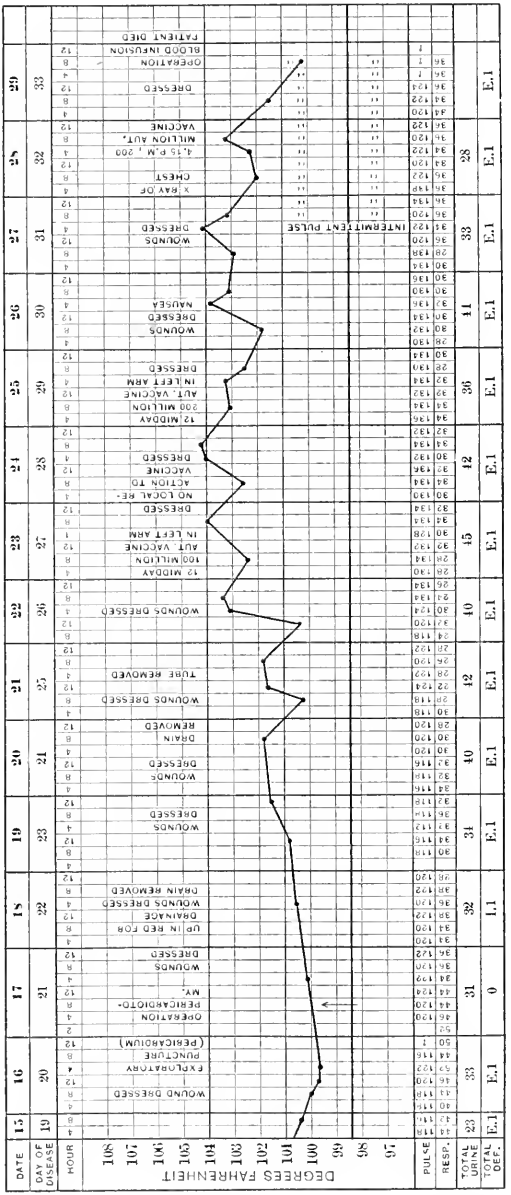
[1] Surgical Treatment of Suppurative Pericarditis, Tr. Am. Surg. Assn., 1897, xv, 101.
[2] Ann. Surg., 1900, xxxii, 769.
[3] Ibid., 1909, xlix, 60.
[4] Ibid., 1915, lxii, 660.

34; pulse, 105. He was put to bed and preparations made for possible pneumonia, which on the next day, December 31, gave frank signs at the lower right lobe. The blood count showed



hemoglobin, 85 per cent.; red blood cells, 4,900,000; white blood cells, 10,000. The differential count showed 85 per cent. polynuclears. Urine showed a specific gravity of 1.031, otherwise

negative. The temperature ranged between 104° and 105° for two days, falling to between 102° and 104° on the following two days, remaining at 102°, with one slight rise, for the following four days.



On January 8, the twelfth day of the disease, it was noted that the tubular quality of inspiration and expiration was more intense along a transverse line at the level of the angle of the scapula, with a

diminishing intensity toward the base of the lung. An exploratory puncture on this date revealed a thin, purulent exudate. Thoracotomy and drainage were performed immediately by one of us (Pool). Cultures from this exudate yielded Staphylococcus pyogenes aureus, from which vaccines were prepared. Patient did well for the next eight days, temperature gradually falling to 99.3°. On January 10 the following note was made: "Heart action strong and regular, no dropped beats. The rhythm is clock-like, there being no rest periods." On January 11 the following nurse's note: "Respirations labored most of the day. Pulse feeble and intermittent. Breathing better upon loosening dressing." January 15 and 16 showed a distinct change in pulse, somewhat irregular and weaker. On January 16 the color of the skin was noted as bad and the respirations labored. Physical signs suggested pericardial effusion, which was confirmed by exploratory puncture; a thin, purulent exudate being obtained, which on culture (by Dr. Mortimer Warren) revealed the same organism as that found in the pleura. The opening and draining of the pericardium was now considered as offering the only chance of relieving the severe cardiac embarrassment. This was done under local anesthesia by one of us (Pool) by the method described in the discussion below. While the patient's condition was critical during the operation, his color and pulse improved markedly the moment the pericardium was relieved of the purulent effusion. He continued to do well for six days following the operation, the pulse, however, being somewhat irregular and at no time forcible. The respirations occasionally became labored, but were always relieved after dressing the pericardial wound. On January 22 the calf of the right leg became painful and swollen, and it was evident on examination that phlebitis had developed. Blood culture at this time showed Staphylococcus aureus. On the evening of the 22d the heart action and breathing became greatly embarrassed, and the following note was made: "Temperature has steadily risen since operation; pulse weak; no heart sounds audible; drainage poor. Digital examination into the wound showed heart sealed to pericardium. Finger introduced deeply in wound, and fresh adhesions broken up, yielding a copious discharge of very thick stringy material and much pus. Patient's condition markedly improved and the heart sound became distinctly audible." On January 23 and 24 respiration and heart action remained good, and the drainage from the pericardium free. On January 26 the pulse became small and intermittent and there was considerable nausea. On January 27 the temperature reached $104\frac{2}{5}°$, falling to 102° on January 28. On this date the chest was radiographed. The report of the findings is as follows:

Indications of fluid and some air in the right pleural sac, with partial collapse of the lung. The heart shadow is distinctly enlarged, suggesting fluid in the pericardium.

Autogenous vaccines were employed, but it was realized that these were used too late in the disease to markedly influence its course. On January 29 the patient died.

Paracentesis Pericardii as a Diagnostic Adjuvant. Although this procedure exposes to the danger of accidental injury to the heart, coronary artery or vein, pleura, lung or internal mammary artery, it must be emphasized that serious accidents have occurred so infrequently that there should be no hesitancy in performing paracentesis when the operation seems definitely indicated. The limitations of exploratory puncture should be definitely appreciated. Even when fluid is present, puncture has often proved unsuccessful. A dry tap may result from the needle becoming blocked with fibrin or with tissue that has been penetrated during its introduction. Moreover, the exudate, especially early, may lie in such a position as to be out of reach of the needle. If suppurative pericarditis is suspected, diagnostic punctures should not be made repeatedly; when several attempts have been made, puncture should be abandoned in favor of pericardiotomy. It must be stated that a number of writers decry the use of puncture for diagnostic purposes. Rhodes states that it can be of positive danger and is usually superfluous.[5]

Opinions differ widely as to the point of election in paracentesis of the pericardium. The favorite sites for punctures fall into two groups: those which are planned to avoid the pleura and those which disregard the pleura, but which are planned to avoid the heart. Under normal conditions the pleura can be avoided by introducing the needle in the region of the sixth and seventh cartilages of the left side, close to the sternum or below the tip of the xiphoid. On the other hand, cardiac injury is best avoided by puncture at a point situated somewhat internal to the lower part of the left limit of pericardial dulness. Curschman advocates this site in preference to one in the immediate vicinity of the cardiac margin or apex, because the effusion is very frequently associated with an enlarged heart, in which case the heart may extend beyond the apparent position of the apex; moreover, it is at times adherent to parietal pericardi. The disadvantage of the outer site is that the pleural cavity may be entered, a feature which is especially disadvantageous in the presence of suppurative pericarditis, but penetration of the pleural cavity is not a necessary complication, because the pleural edges are separated by the distended pericardium, and not infrequently the pleural layers are agglutinated to a considerable degree by adhesions, causing obliteration of the anterior part of the pleural sac.

The following sites are most suitable for paracentesis of the pericardium:

[5] Some features in this article are taken, with permission of the publishers, from Johnson's Operative Therapeusis: Heart and Pericardium, by E. H. Pool, published by D. Appleton & Co.

1. A point slightly internal to the left limit of dulness, in the fifth or sixth intercostal space.

2. Midline immediately below the xiphoid process. This situation is recommended by François and others as the point of election for entrance, because here the pericardium is reached by the shortest route without injury to bloodvessels, pleura, and peritoneum, while the exudate can be evacuated before the heart is touched. The only contra-indications of this method are extreme malformations of the sternum and a high degree of tympanites. Under local anesthesia a fine trocar or hollow needle of sufficient length is inserted and pushed directly upward to a distance of 2 cm. along the posterior surface of the xiphoid. In this way the peritoneum is avoided, and after passing through the diaphragm the point of the needle is directed upward and backward.

3. A point in the angle formed by the base of the xiphoid process and the seventh left cartilage at its insertion. The choice between these sites must depend upon individual indications.

Pericarditis occurs as a relatively frequent complication in a large number of diseases, the most frequent of which are inflammatory rheumatism, nephritis, pleurisy, pneumonia, pyogenic infections, and tuberculosis, but there are "few infectious diseases which may not implicate the pericardium." (MacPhedran.[6])

The clinical picture of pericarditis with effusion is variable. Besides the local objective signs, the cardinal sign of exudative pericarditis being a characteristic cardiac dulness which is at first increased upward, there are present to a variable degree, symptoms due to: (1) involvement of the heart muscle (myocarditis), which is the most frequent and serious lesion; (2) endocarditis (these two are especially frequent in association with rheumatism); (3) mechanical disturbance of the heart as a result of pressure exerted by the effusion; this, however, is infrequent; (4) general constitutional disturbances, depending upon the type of the infection, the pericardium offering a large surface for absorption; (5) an associated lesion or disease.

Suppurative pericarditis represents an abscess corresponding to a part or the whole of the pericardial sac. The most frequent organisms are the streptococcus, staphylococcus, and pneumococcus. The exudate is usually purulent from the beginning of the attack, although occasionally it develops in the course of a non-suppurative pericarditis. As a rule, purulent pericarditis is secondary in the course of a pyogenic infection, and under such conditions it frequently constitutes a "terminal infection;" in rare cases suppurative pericarditis is primary; in some cases the infection is introduced through a wound.

Suppurative pericarditis is characterized by the local sign of

[6] Osler's Modern Medicine, iv, 40.

pericarditis, with effusion and constitutional symptoms of a septic character. The fact that the pericarditis is frequently a secondary lesion causes its presence to be overlooked in many cases. In children the symptoms of pericarditis are particularly apt to be masked. On the other hand, in many cases in which the lesion has recognized and the pericardium drained, the operation has been unsuccessful because a coexisting purulent focus, especially empyema, has been overlooked. It follows that in septic processes it is necessary to watch for the development of pericarditis; moreover, the recognition of such a condition should not cause less thoroughness in the search for other foci.

The distribution of the fluid in the distended sac must be understood in order to appreciate the technical details of paracentesis or pericardiotomy. First, the recesses become filled, the fluid gathering chiefly in the region of the base of the heart; then the bulging pericardium, confined anteriorly, separates the yielding lungs and pushes the diaphragm downward. The increasing exudate progressively distends the pericardium, for the most part to the left and posteriorly It must be emphasized that the heart usually, though not invariably, occupies a low position and remains applied to the anterior wall of the thorax. Occasionally an inflammatory process may become localized by the formation of adhesions and the limitation of the exudate to a circumscribed part of the sac.

Pericardiotomy. The methods of pericardiotomy may be divided for convenience into two groups:

1. Procedures which reach the pericardium through the thoracic wall.

2. Procedures which enter from below the costal arch, the epigastric route.

The first method of procedure includes:

Resection of the sixth cartilage, as recommended by Kocher, Axhausen, and Pels-Leusden.

Resection of the fifth cartilage, Gussenbauer and Ollier.

Resection of the fifth and sixth cartilages, Delmore and Mignon.

The second method of procedure has been accorded the preference by Larrey, Mintz, L. Rehn, and Allingham. The approach is in part or entirely from below the costal arch, and is both extra pleural and extraperitoneal.

Pericardiotomy for the Evacuation of a Purulent Exudate. In the treatment of suppurative pericarditis the method of pericardiotomy to be efficient must provide for satisfactory drainage, and be sufficiently simple to be rapidly performed under local anesthesia if necessary. Adequate drainage is the essential feature, and upon this must depend, to a large extent, the choice of method. In the interest of good drainage it is important (1) to open the pericardium at its lowest point, and (2) to provide such an opening as will ensure ready egress for accumulation of fluid in both the

right and left spaces of the pericardial sac. Local anesthesia is frequently imperative because the heart is apt to be dilated and insufficient as a result of endocarditis and myocarditis. It is necessary that the work be done with the least possible associated injury. It is not sufficient to avoid wounding the heart; if possible the heart should not be touched. Further, thorough anesthetization of the pericardium is advisable on the basis of significant experimental work, which we will briefly summarize.

Serious disturbances of the heart action have been noted repeatedly to result from irritation of the pericardium. Heitler's[7] observations on dogs showed that irregularity of the heart follows mechanical or electrical stimulation of the pericardium. D'Agata[8] (1912) in animal experiments found that a sudden drop in the blood-pressure occurred as a result of grasping and incising the pericardium. These phenomena are presumably reflex in character; they help to explain analogous clinical observations. Thus, Harrigan[9] reported temporary arrest of the heart upon incision of the pericardium in a case of suppurative pericarditis.

Heitler and D'Agata found in their experiments that preliminary cocainization of the parietal layer of the pericardium prevented the occurrence of irregularity of the heart and the lowering of the blood-pressure. Heitler recommended that before an incision is made in the pericardium it should be anesthetized by means of a 10 per cent. solution of cocain applied to its surface. Presumably novocain by injection could be substituted to advantage in man.

The two methods most appropriate for drainage in suppurative pericarditis will be described in detail.

1. Resection of the sixth costal cartilage. (Kocher.[10])
2. Resection of the seventh, or sixth and seventh costal cartilages (Rehn.)

Resection of Sixth Cartilage. This method affords adequate drainage at a dependent part of the sac, is simple and quick of execution, may be performed readily under local anesthesia, and the exposure may be extended easily in any direction. It appears the best method for general use and was employed in our case.

With the patient in a semirecumbent position, an incision is made in the course of the sixth cartilage and rib, passing from the midline obliquely outward. The perichondrium is incised in the direction of the wound and separated. The cartilage is then severed close to the sternum and lifted, the perichondrium being separated from its posterior surface. The cartilage is broken at its junction with the rib and removed. The internal mammary artery should be divided between ligatures when exposed. The triangularis sterni is then split. An effort should be made to identify the anterior

[7] Med. Klin., 1910, vi, 974.
[8] Arch. f. klin. Chir., 1912, xcviii, 460.
[9] Ann. Surg., 1913, lvii, 367.
[10] Chirurgische Operationslehre, 1907, xxxiv, 777.

edge of the underlying pleura, which should be pushed outward. The pericardium is thus exposed. It should be grasped and lifted with two pairs of toothed forceps and incised. (The importance of anesthetizing the pericardium has been emphasized above.) The pericardial incision is extended with blunt-pointed scissors. The pus should be allowed to escape slowly. A finger is then introduced to break up adhesions and to evacuate walled-off accumulations of pus. Should the access be too small to allow separation of adhesions, or for adequate drainage, the opening may be enlarged in an appropriate direction by resection of part of the sternum, excision of part of the sixth rib, or removal of the fifth or the seventh costal cartilates. Residual fluid should be removed by aspiration, as in abdominal operations, and sponging or wiping of the serous surfaces should be reduced to a minimum. Clots of fibrin should be extracted with forceps. Irrigation with sterile salt solution has been used for the removal of clots of fibrin, but is not to be recommended. The use of antiseptic fluids is contra-indicated. In closing the wound it is advisable, especially if the pericardium is considerably separated from the sternum, to suture it to the skin. This not only facilitates drainage but "diminishes the risk of contamination of the anterior mediastinum." (Eliot.)

Drainage is favored by the movements of the heart, which in the absence of adhesions tends to force out any accumulated pus (Eliot). The kind of drain which should be used is a detail which demands some discussion. The choice lies between a rubber tube and soft drain. Tubes afford the most satisfactory drainage and may be sutured to the soft parts, so that they are not readily displaced. But if the tube should come into contact with the heart it is likely to interfere with the cardiac action, as occurred in a case operated upon by Riedel.[11] Rehn[12] recommends two rubber tubes, one passing to the right side and one to the left to drain both pockets. Eliot, Riedel and others favor soft drains. A general rule cannot be made, as the mode of drainage must be such as to fit the individual case.

Two cigarette drains were employed in our case. They did not drain satisfactorily. We are of the opinion that split soft rubber tubes would have been better.

The sitting position should be enforced in the after-treatment as most favorable for drainage. The wound heals, as a rule, without a persistent sinus, and "after healing is complete, insufficient or irregular heart action is the marked exception; neither is there any indication of cardiac displacement." (Eliot.)

Resection of the Seventh or Sixth and Seventh Costal Cartilages. A curved incision of about 6 cm. is made along the lower margin

[11] Zentralbl. f. Chir., 1897, xxiv, 56.

[12] Zur experimentallen Pathologie des Herzbeutels, Arch. f. klin. Chir., 1913, cii, 1; Berl. klin. Wchnschr., 1913, i, 214; Zur Chirurgie des Herzens und des Herzbeutels, Arch. f. klin. Chir., 1907, lxxxiii, 723–778.

of the seventh left cartilage to the base of the ensiform process, across which the incision is continued transversely. The incision is deepened and the seventh costal cratilage divided. The internal mammary artery is preserved. Detaching the soft parts, the finger is passed under the sternum, between the lower portions of the triangularis sterni muscle and the sternal portions of the diaphragm. A piece of the sternum and seventh costal cartilage is removed, followed by resection of the sixth costal cartilage if necessary. The pericardium is readily reached without opening the pleura. The more distended the pericardium the easier the operation. (Description after Kuttner.[13])

Prognosis. Suppurative pericarditis demands immediate incision and drainage. The prognosis in purulent pericarditis is in general unfavorable, yet in suppurative processes which are confined to the pericardium early operation is quite often followed by recovery; on the other hand, when the pericardium is involved secondarily in the course of a general sepsis, recovery is infrequent. Nevertheless, cases that appear hopeless are occasionally saved by operation. As mentioned below a prognosis must depend largely on the characteristics of the organism causing the disease, but as yet this has not been studied with sufficient accuracy to consider it in this report.

Conclusion. The results of pericardiotomy are necessarily modified by the gravity of the fundamental disease, but striking cures have followed operation in apparently hopeless cases of severe infection. In studying our case, together with the literature here quoted, the need for a bacteriological division of these cases seems imperative. From Rufus Cole's work we now have a new aspect of the clinical condition known as pneumonia. This new view-point is bacteriological in character. We now know that the anatomical diagnosis of consolidation of a lobe, or of a purulent accumulation in the pleura or pericardium may be correct, and yet the clinical course vastly different according to the organism producing the condition. In traumatic injuries to the pericardium when operation has been successfully performed and recovery has followed, the favorable factor is probably the absence of bacterial infection. In our case a most virulent organism, the staphylococcus, was the cause of a bacteriemia. Was the dose and virulence of the toxin so overwhelming that no known method would have been sufficient to overcome these? Perhaps vaccines should have been used from the time of the furunculosis, but at that time no culture was taken and there was prompt recovery from a single abscess in the neck. The question naturally arises as to whether we should regard these simple abscesses as demanding immediate vaccine treatment as a routine, fearing the development of larger areas of pus in more vital localities.

[13] Bier-Braun-Kummell, Chirurg. Operationslehre, 1912, ii, SS.

Is pericardiotomy justifiable or imperative in all cases of suppurative pericarditis? As to the justification for pericardiotomy in all cases of suppurative pericarditis it would seem that the operation should be performed as an emergency procedure even in desperate cases. The importance of an early diagnosis cannot be too strongly urged. Whether exploratory puncture reveals a purulent or a non-purulent effusion, cultures should be made and an accurate report presented. We may expect that further bacteriological studies will throw light upon the general clinical course due to different types of organisms. Thus the prognosis in a given case may be made more exact and the indications for surgical intervention may be further developed. This case and those quoted from literature go to emphasize the fact now being grasped by the profession that pneumonia is a local manifestation of a systemic infection, and in dealing successfully with it measures capable of reaching the antigen power of the system must be sought and employed.

THE FOLLOWING CASES FROM LITERATURE ARE ARRANGED AS FOLLOWS:

Suppurative pericarditis following: (1) pneumonia; (*a*) lobar; (*b*) broncho. (2) Empyema.

A bacteriological division is not possible, as cases have not been studied accurately with this feature especially considered. This is a most important aspect of suppurative pericarditis and offers a field for future investigation. From the data in some of the following reports it is difficult to determine whether pneumonia was clinically present.

1. Pneumonia: (*a*) lobar.

Female, aged forty years. Croupous pneumonia, empyema, and purulent pericarditis. Thoracotomy for empyema; six days later pericardiotomy, Ollier's method. Fifth rib resected. Pericardium opened 400 to 450 c.c. of pus with fibrinopurulent exudate evacuated. Drainage tube introduced and held by suture. After operation patient in collapse and cyanotic. Gradual recovery. (Original article not accessible.) (Tallquist; cf. Rhodes.[14])

Boy, aged twelve years. Bilateral diplococcus pneumonia. Ill for about two weeks and was in bad condition before the operation, heart dulness extending two fingers' width beyond the right sternal margin and to the midaxillary line on the left side. Incision along the lower margin of the seventh costal cartilage. A skin and cartilage flap formed which was turned upward, permitting access to the space through which the pericardium could be opened without injuring the pleura; 100 c.c. of seropurulent fluid was evacuated, and a tampon introduced. General condition continued to improve;

[14] Finska laksallsk. Handl. Helsingfors I, 1912, 575-595.

patient discharged after about two months, with normal heart boundaries and without any disturbance except a fistula from which a small amount of pus escaped. (Mintz.[15])

Boy, aged five years. Bilateral croupous pneumonia. Apex beat could not be felt; the heart sounds were very faintly audible. Dulness two fingers' width beyond the right sternal margin and a finger's width beyond the nipple-line to the left side. Exploratory puncture in the fifth intercostal space yielded 60 cm. of thick fluid pus, and was followed by visible improvement. Pericardiotomy, with resection of the fifth costal cartilage, according to Ollier. Half liter of pus escaped. The heart was found lying behind and above, floating free in the large cavity. Subperichondral resection of the fourth costal cartilage was added. Drainage with rubber tube the thickness of a thumb. In three weeks cavity had entirely disappeared without leaving a thoracic deformity. Good recovery.

The author emphasizes the advantages of pericardiotomy with costal resection on the basis of Terrier's statistics, and recommends early operative interference, which has a simple technic as in empyema and yields the best results as to life and rapid healing. (Strauss.[16])

Pericarditis secondary to double pneumonia. The pericardium was opened in the midaxillary line and a large amount of pus was evacuated. A few days after the operation there were signs of pus farther back, and an incision there revealed an empyema. The patient died. (Blake.[17])

Boy, aged nine years. Left-sided pneumonia. On the ninth day dulness was noted, extending on the right side one finger's breadth beyond the right sternal margin; on the left side two fingers' width beyond the left maxillary line. Heart sounds inaudible; superficial veins of thorax much distended, especially on right toward shoulder. Pericardiotomy was performed by v. Eiselberg, in spite of the patient's apparently moribund condition. Resection of fifth costal cartilage. Exploratory puncture of bulging pericardial sac yielded pus. Transverse incision of pericardium; escape of about one liter of thick yellow pus. Two rubber drainage tubes. Pulse was plainly palpable three hours after operation. General condition rapidly improved. A fistula persisted for nine weeks. Recovery. Bacteriological examination of the pus showed streptococci. The patient was reëxamined nine years after operation and was found to be in good condition. (Walzel.[18])

Man, aged thirty-one years. Pneumonia chiefly involving the

[15] Chirurgia, April, 1912, vol. xxxi (Russian); Centralblatt f. Chir., 1912, No. 30, p. 1046.

[16] Nuremberg Med. Soc., meeting of July 15, 1909; München. med. Wchnschr., 1909, No. 39, p. 2039 (or 7).

[17] New York Surgical Society, October 28, 1908; Annals of Surgery, 1909, xlix, 142.

[18] Mittlg. a. d. Grenzgeb. d. Med. u. Chir., 1913, xxv, 264.

left lung. Three weeks later cardiac dulness four fingers' breadth to the right of the sternum, with muffled heart sounds, persistent high temperature, considerable cyanosis, and dyspnea. Pericardium was incised, after removal of the seventh costal cartilage and a portion of the sixth; 3 to 4 ounces of fluid were withdrawn. Numerous adhesions between the right heart and parietal pericardium were broken down and a tube was inserted, which was removed on the sixth day after the operation. The patient made a good recovery. (Pandlebury; cf. Eliot.[19])

Male, aged thirty-six years. Bilateral pneumonia. On the thirteenth day the pericardium was considered involved. Twenty-first day the cardiac dulness was decidedly increased in all directions, especially toward the right. Exploratory puncture yielded a turbid greenish fluid. On culture a pure growth of pneumococci. Incision of pericardium and evacuation of about a pint of pus. Examination showed pneumococci. Drainage tube removed twenty-six days after operation and the patient left the hospital fifty-one days after operation, free from physical signs of an adhesive pericarditis. (Scott; Eliot.[20])

Woman, aged thirty-eight years. Puerperal sepsis and double pneumonia, three weeks before admission to the hospital. Extensive area of cardiac dulness, the heart sounds being almost inaudible. Puncture of the pericardium in the fourth intercostal space yielded pus. Excision of the fourth left costal cartilage with evacuation of 20 ounces of grayish-yellow pus. Drainage, with profuse discharge, until death one week after the operation, probably due to suppurative peritonitis.

Examination of the pus from the pericardium showed various streptococci and staphylococci. (Hall; Eliot.[21])

Patient, aged two and a half years. Pneumonia a month before admission to the hospital, when the diagnosis was made of a probable empyema at the right base, with a purulent pericarditis. Chloroform anesthesia. Oblique incision exposing the fifth left cartilage, which was removed in part with adjacent part of sternum. Incision of the pericardium with evacuation of about half a pint of thin greenish-yellow pus under pressure. A rubber drainage tube was inserted. Pericardial fluid contained a coccus which resembled pneumococcus. Temporary improvement. The empyema pus, obtained by operation on next day, showed a coccus which resembled the pneumococcus; other forms of cocci and bacilli were also numerous. The patient died in the sixteenth week after the operations.

Necropsy. On opening the thorax there was found a condition of universal dense adhesion of the contained viscera to each other and

[19] Lancet, October 22, 1904, p. 1144.
[20] New York Med. Jour., January 30, 1904, p. 198.
[21] Lancet, 1903, ii, 951.

to the chest wall, and the whole anterior mediastinum was occupied by a thick fibrogelatinous deposit. The wound over the pericardial area drained a small pocket on the anterior surface of the heart, but elsewhere the pericardium was inseparably adherent to the heart in front. On attempting to separate the pericardium from the left lung an abscess cavity was opened, with a discharge of 3 ounces of pale thick pus. This cavity lay behind, and to the left of the heart and within the pericardial sac; its walls were very thick from the presence of fibrinous matter similar to that occupying the mediastinum. Between the heart and the right lung there lay another smaller cavity, independent of the first, and full of inspissated pus. The pus in both cavities was dry and gritty to the feel, as if impregnated with lime salts. The tracheal glands were greatly enlarged, but free from all sign of tubercle. The pleuræ were everywhere adherent. (Coutts and Rowland; Eliot[22].)

Boy, aged sixteen years; sore throat, followed a day or two later by most of the symptoms of pneumonia of the left base without very distinct physical signs. At the end of three weeks, a left empyema was opened, without much relief to the general symptoms. Ten days afterward, the pericardium was opened, with only slight temporary general improvement. Death thirteen days after incision of pericardium, apparently due to external hemorrhage from the heart through rupture of a small parietal abscess.

Bacteriological examination proved the presence of pneumococci in great numbers in the blood, death being the result of a general pneumococcus pyemia. (Sibley, Arbuthnot Land and Rowell; Eliot.[23])

Pericarditis developed after a severe (left-sided) pneumonia. Aspiration showed the presence of a purulent effusion. Thirty ounces of the fluid were removed by aspiration. Pericardiotomy under local anesthesia, nearly 40 ounces evacuated. The pleura was slightly incised at the operation, and probably became infected, although it was at once carefully closed. The patient's condition at once improved and the alarming acute symptoms disappeared. The right pleura extended beyond the sternum, owing to the compensatory hypertrophy of the right lung, because of the pneumonia in the left. The accidental incision of pleura probably followed by infection. Patient died of purulent pneumonia a few days later. (Connor, L. A.; operator, Stimson.[24])

Male, aged fifteen years. Severe double lobar pneumonia. Pericardial friction sound heard on the fourteenth day. No increase of heart dulness could be demonstrated for two days, however. Ten days later the patient was in very bad condition and was aspir-

[22] Brit. Med. Jour., 1904, i, 9.

[23] Ibid., May 23, 1903, p. 1192.

[24] Med. News, January 20, 1900, lxxvi, 115; New York Academy of Medicine, stated meeting, December 19, 1899.

ated for the pericarditis, with removal of 18½ ounces of pus. This was found to contain a pure culture of the pneumococcus. No improvement. Operation under local anesthesia, incision from third to fifth intercostal space; resection of three-quarters of an inch of the costal cartilages. Penetration of pericardium was at once followed by a tremendous gust of pus, estimated at 50 to 60 ounces. Wound was left open; no artificial drainage. Irrigations with normal salt solution. Patient in excellent general condition three months after the operation. Bacteriological examination showed pneumococcus in pus in pure caulture; pneumococcus and streptococcus in sputum. (Lilienthal, H.[25])

Male, aged twenty-four years. Lobar pneumonia. Sudden attack of chills and fever; followed by dyspnea and pain in left half of chest. Exploratory puncture. Incision in middle of fifth intercostal space, between sternum and nipple. Incision showed the existence of pleural adhesions. The pericardium was opened, and a large stream of pus spurted out. Patient was in collapse, but recovered after digital massag of the heart. The fluid had a greenish color, contained some fibrin flakes, and amounted to about 1½ liters. A thick long drainage tube was inserted, reaching to the back portion of the pericardium. After a fortnight, careful irrigations of the pericardial cavity with salt solution were begun and repeated every third day, to wash away the fibrin coagula, but it finally became necessary to do a resection of the fifth rib, in order to obtain a freer access to the pericardium and break up adhesions. After this, recovery was rapid; fistula closed a month later. Patient discharged in good condition, about five months after admission to the hospital.

No bacteriological growth from original fluid; microscope showed small, short bacilli often lying two or three together. Bacillus pyocyaneus grew in all cultures made from the discharge after operation. (Ljunggren, C. A.[26])

Male, aged twenty-two years. Acute pneumonia. Pericardiocentesis; incision in fourth left interspace, under cocain. Forty-five ounces of pus escaped. Irrigation with boracic acid. Tube drain. Temporary improvement was followed by purulent effusion in both pleural cavities. Bilateral costal resection and escape of 35 ounces of pus. Pneumococci were present in the pus from both pleural cavities. The pus from the pericardium showed almost a pure culture of pneumococci. Death one month after admission to the hospital. (Sevestre, R.[27])

Male, aged twenty-two years. Purulent pericarditis due to pneumonia. No pericardial friction. Double empyema. Aspiration fourth space one inch from sternum; incision in same place. Evacu-

[25] Med. News, 1899, lxxv, 697. Presentation of case, New York Academy of Medicine, Section on Surgery, November 13, 1899.

[26] Nord. Med. Arkiv., 1898, ix, 1.

[27] Lancet, April 23, 1898, i, 1109.

ation of large amount of pus. Death eighteen days after operation. Autopsy findings: Thickened pericardium; double empyema. (Bradbury, quoted by Sevestre.[28])

Boy, aged fourteen years. Pleuritis, pneumonia. Abscess of thigh, acute arthritis of left shoulder. There was much dyspnea and some cyanosis, and there were physical signs of pneumonia of the base. The left pleura was tapped, but only a few ounces of serum were evacuated; from the pericardium 24 ounces of pus was drawn off. Though relieved for a time the dyspnea and cyanosis returned, and the patient died. (West, S.[29])

Boy, aged six years. Pyemia and septic pneumonia after necrosis of metatarsus. Pus having been shown by aspiration, the fifth interspace was incised and 8 ounces of pus evacuated, no irrigation. Drainage tube of $3\frac{1}{2}$ inches. Temporary relief, but rise of temperature on next day (104° F.). Patient lived seven days after the operation. (Davidson, P.[30])

The author says that this case resembles Bronner's observation in several points, viz., in the occurrence together of pleurisy, pneumonia, and pyopericarditis, also in the character of the pneumonia, sometimes called "wandering pneumonia;" and in the rise of temperature after the opening of the pericardium.

Boy, aged six and three-quarter years. Admitted with history of a fortnight's illness, with cough, fever and pain in the left side. Pus was obtained on exploratory puncture in left pleural cavity. Next day, thoracotomy and removal of 10 ounces of pus. Drainage. Increasing precordial dulness. Exploration of pericardium yielded pus. Incision in fourth interspace; escape of several ounces of creamy pus. Tube drain. Pericardium and empyema took about five weeks to heal. Patient was discharged in good condition two months after admission.

Girl, aged eleven years. Influenza, pneumonia, and empyema. Thoracotomy of right pleura pericardiotomy. Incision in fourth space one inch from sternum; escape of 2 pints of thick pus. Irrigation: short tube drain. Pericardial cavity was syringed out on eleventh day after operation. Death twenty-six days after the incision into the pericardium, on the sixtieth day of illness. No bacteriological examination of pus. Bronner says that the pneumonia resembled Ribbert's streptococcus pneumonia, characterized by great irregularity of the percutory and auscultatory symptoms, by a tendency to spread, and by irregular infiltration of the lung tissue on postmortem examination. (Bronner; operator, Teale.[31])

Female, aged twenty-two years. Right-sided pneumonia and right empyema pericardiocentesis. Seven days later pericardio-

[28] Lancet, 1898, i, 1111.
[29] Brit. Med. Jour., December 8, 1883, p. 1129; February 21, 1891, p. 404.
[30] Ibid., March 14, 1891, p. 578.
[31] Ibid., February 14, 1891, p. 350.

tomy; incision in third space near sternum. Escape of large amount of purulent fluid. Drainage. No irrigation. Left empyema after operation. Death (pyemia) on thirteenth day after pericardiotomy. Bacteriological findings: Bacilli in pus, small short ends, neither pneumococci nor streptococci. Autopsy findings showed pus in pericardial and both pleural cavities, as well as acute nephritic changes. (Sievers, R.[32])

Male, aged twenty years. Right lobar pneumonia; pleural and pericardial effusion. Aspiration. Incision in fourth intercostal space, between nipple and sternum, on thirty-fourth day. No irrigation. Tube drain, free outflow of pus. Death from heart failure in thirty days, after pericardiotomy, and sixty-fourth day of illness. Bacteriological findings: Fraenkel's diplococcus in pus discharged from wound. (O'Carroll, J.[33])

Male, aged thirty-three years. Influenza pleuropneumonia followed by purulent pericarditis. Tapped three times. Incision in third intercostal space; pus under high pressure escaped on incision of pericardium. Local anesthesia (Schleich). Irrigation, boric acid, gauze drain. Immediate relief and improvement. Recovery in four and a half weeks. Discharged from hospital three months after the pericardiotomy. No bacteriological examination of pus. (Bohn, H.[34])

Male, aged twenty-six years. Pneumonia. Pericardial effusion. Left empyema. Pericardiocentesis; incision in fifth left space $1\frac{1}{2}$ inches to left of sternum. Large amount of pus evacuated. Irrigation with salt solution. Drainage with two tubes. Resection of fifth rib, six days later, for better drainage. Empyema; pneumothorax after operation. Recovery. Bacteriological findings: Pneumococcus in pus from pericardium and empyema. (Shattuck, F. C.; operator, Porter, C. B.[35])

Girl, aged twelve years. Influenza and pleuropneumonia. Paracentesis of pericardium. Resection of fifth and sixth ribs; pleura opened and sutured after evacuation of some bloody serum. Irrigation with boric acid solution; drainage, two large tubes. Recovery in six weeks. No bacteriological examination of pus. (Björkman; quoted by Roberts.[36])

(*b*) Broncho:

Boy, aged ten years. Twelve days before admission he fell forcibly upon the left anterior part of his chest. Three days later felt sick and complained of pain in the left side.

Examination. Fever, cough, dyspnea. Temperature, 39°; pulse, 130; respirations, 36; rather diaphragmatic, and left side of thorax

[32] Ztschr. f. klin. Med., 1893, xxiii, 26.

[33] Dublin Jour. Med. Sc., 1896, cii, 11; Same case as that of O'Carroll in Tr. Royal Acad. Med., Ireland, 1896, xiv, 106.

[34] Deutsche med. Wchnschr., 1896, xxii, No. 48, 769.

[35] Boston Med. and Surg. Jour., 1897, cxxvi, 438.

[36] Am. Jour. Med. Sc., 1897, cxiv, 662.

remaining immobile in respiration. Dulness on left from clavicle embracing, below, the precordial area, and extending one finger's breadth beyond right sternal line. On the left the dulness continues to axillary line. Signs of fluid in left pleura. Bronchopneumonia and congestion.

Diagnosis. Pleuropericarditis. Aspiration in seventh space, axillary line. No result. Condition gradually worse, with abdominal and precordial pain, loss of sleep from pain and cough. Streptococci in expectoration. Nine days after entrance into hospital an aspiration through fifth left intercostal space in mammary line; pus withdrawn. Operation. Incision 4 cm. long in fifth intercostal space, commencing 1 cm. from left sternal margin. Down to pericardium. Aspirated 250 grams of pus. Cultures showed white colonies, Gram-positive. Rapid fall in temperature.

Patient had a stormy time with the bronchopneumonia, but left the hospital with normal heart outlines and good action. No retraction of intercostal spaces. (Björkman; Imerwol; cf. Rhodes.[37])

Boy, aged eight years. Admitted as a case of appendicitis. Tentative diagnosis was bronchopneumonia, affecting principally the left lung, with possible pericardial effusion. Three days later pericardial paracentesis; $6\frac{1}{2}$ ounces of thick purulent fluid withdrawn, giving almost immediate relief. Two days later pericardiotomy, after resection of part of fifth rib about $1\frac{1}{2}$ pints of pus evacuated. Drainage tube inserted; discharge free. After first gaining some strength, the patient slowly lost ground, under symptoms of pyemia. Death. Examinations of the purulent discharge showed a double coccus (thought not to be pneumococcus by laboratory interne). Examination of the sputum for tubercle bacilli and pneumococci was made with negative results. According to the postmortem report, the left lung was totally collapsed and compressed to a very small size into the apex of the left chest. In the base of the right lung there was a cavity about the size of a walnut, containing bloody purulent fluid. No communication between the pericardium and lungs or pleura. The collapsed left lung was explained by the fact that the pleura was probably accidentally opened during the operation. (Gengenbach, F. P.; cf. Eliot.[38])

Boy, aged four years. Severe bronchopneumonia. Pericardiotomy. Resection of fifth cartilage; pleura not opened. Seropurulent fluid and typical pus from deepest part of sac, about 10 ounces. No irrigation; gauze drain. Death in three days. There was no evidence of, and no history to suggest that the whole condition was pyemia. The pus from the pericardium gave on cultivation an almost pure growth of Friedländer's pneumococcus. (Robinson, H. B.; Case II.[39])

[37] Hygeia, 1896, lviii, 189; Am. Surg., 1915, lxii, 660.
[38] Colorado Med., 1906, iii, 198. (A case of purulent pericarditis.)
[39] Brit. Med. Jour., November 26, 1898, ii, 1605.

2. Empyema.

Male, aged twenty-eight years. About January 7, 1913, when working, he developed pain in the right side, shortness of breath, cough, and tenacious sputum, and came to hospital for treatment. Temperature, 102.4°; right lower lobe dull. Crepitant rales and bronchial breathing.

January 14, complained of pain in right side, also pain in precordial region. Pericardial friction rub heard.

January 31, needle introduced in sixth interspace just beyond apex of heart and a quart of pus drawn off.

Operation. Ransohoff. Local anesthesia (cocain). Sixth rib, 2 inches or rib resected, starting one-half inch from sternum. Pericardium punctured and pus drawn off. Pericardium opened liberating about 3 pints of a fairly thick yellowish pus. Pericardium stitched to thoracic wall and gutta-percha drain inserted.

March 5, patient died.

Autopsy. Right lung showed congestion and an infarct in lower portion of middle lobe; pleura normal. Left pleural cavity contained about a quart of greenish pus, and the lung was found compressed into upper part of pleural cavity. It showed infarction and congestion.

Pericardial sac was entirely obliterated except posteriorly below and anteriorly where drainage had been established.

Pancreas, spleen and alimentary canal normal.

Left kidney showed a total infarction due to thrombosis of renal artery. Right kidney was congested. (Ransohoff; cf. Rhodes.[40])

Boy, aged nine years. Two weeks before admission had chills and fever, pain in left side of thorax, fever high.

Diagnosis. Exudative pericarditis and pleurisy.

May 5, aspiration in axillary region, fifth interspace, gave pus from left plura.

May 6, aspiration in anterior axillary line, fifth left interspace 300 grams, seropurulent fluid. Aspiration of pericardium, fifth left interspace $3\frac{1}{2}$ cm. from left sternal border gave pus. Improvement.

May 19, thoracotomy in fifth left space, axillary line; 350 grams of pus, drainage tube.

May 20, discovered that the pericardium opens into the left pleura by an orifice. Heart sounds audible and apex beat visible. For the next four days this orifice increased in size. Case gradually improved and discharge lessened. Drains removed July 15 and gauze substituted. Wound cicatrized.

July 20, no retraction of intercostal spaces. Normal. Pus showed pneumococci. Imerwol, V.; cf. Rhodes.[41])

Girl, aged six years. Empyema; thoracotomy. Pericardiotomy. Incision one-half inch within and above apex beat. Nine ounces of pus removed. No irrigation; tube drain. First improvement; two weeks later aggravation of condition in spite of good drainage.

[40] Ann. Surg., 1915, lxii, 660.

[41] Ibid., lxiii, 660.

Incision was now made in the eighth interspace at the post-axillary line, 16 ounces of pus were removed, and a tube was inserted. Resection of a portion of three ribs was done later. The patient died within a week after the last operation. In the light of post-mortem knowledge it appears that this case was a primary mediastinopericarditis, which within two months was followed by a purulent pleurisy. It would seem that the child presented a primary inflammation of the entire anterior mediastinum, which included the pericardium; the empyema was concomitant through continuity. (Edwards, W. A.[42])

Patient was a soldier with left-sided pleurisy following influenza. Empyema. Incision in sixth intercostal space; demonstration of general pleurisy, with considerable retraction of the lung. General improvement followed, but dyspnea persisted and became greatly aggravated three days after the operation. Paracentesis. Pericardiotomy. Incision 6 cm. in fourth intercostal space; escape of only a few drops of turbid fluid. Patient succumbed to asphyxia a few minutes later; the operation having been too long delayed.

Autopsy findings showed that anterior wall of heart was adherent, about a pint of pus was found behind and at the sides of the adherent heart. (Delorme and Mignon.[43])

Boy, aged seven years. Pericarditis, followed by empyema. Pericardium was reached through left fourth interspace, and a considerable quantity of seropurulent fluid. Drainage tube. Considerable improvement. The fluid removed was albuminous and coagulable, and contained Staphylococcus pyogenes aureus. Empyema subsequently developed, fluid aspirated contained the Staphylococcus pyogenes aureus. Thoracotomy yielded 30 ounces of pus. Good recovery. (Peters, G. A.[44])

Male, aged thirty-six years. Old purulent encysted pleurisy, no acute course. Resection of two inches of fifth cartilage; pleura not opened; incision of pericardium; escape of 15 to 16 ounces of pus. Irrigation with hot water; edges of pericardium were sewed to skin.

Death from weakness in fourteen hours. According to the post-mortem findings the origin of the pericardium appeared to be a collection of pus lying close to the right of the sac between it and the lung and the chest wall, which was the result of a previous pleurisy. (Ogle, C., and Allingham, H.[45])

Boy, aged eleven years. Old empyema. Resection of the sixth rib below and inside nipple. Evacuation of 2 quarts of pus. Irrigation with sterile water, gauze drain. Death in twenty days. Allen; quoted by Roberts.[46])

[42] Transactions of the Medical Society of the State of California, 1893, p. 166.

[43] Rev. de Chir., 1895, xv, 1008.

[44] Edinburgh Med. Jour., 1903, xiii, 209. Purulent pericarditis complicated by empyema; operation and recovery.

[45] Lancet, March 10, 1900, i, 693.

[46] Am. Jour. Med. Sc., 1897, cxiv, 662.

ACUTE PERICARDITIS.

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This paper is based upon a study of the protocols of eighty proved cases of acute pericarditis and the literature particularly of the last five years. It seeks to emphasize certain physical signs which have seemed of importance to the writer.

Most authors, especially the writers of text-books, begin with a history of pericardial lesions. There is no record that Hippocrates observed the condition, but Galen noted it in animals and suspected it in man; various writers mentioned it, but it was not referred to as a clinical condition until described by Senac in 1749. Laennec, the father of auscultation, described a creaking sound over the heart, but it remained for Collin, his chief assistant, to clearly demonstrate the pericardial friction rub and interpret its clinical significance.

Anatomy. It is important for the student of pericardial inflammations to rehearse the anatomy of the pericardium—to have the anatomical relations of the sac to other structures in the thorax in mind is helpful in considering the subjective and objective symptomatology. The pericardium is a conical serofibrous sac enveloping the heart and the first portion of the great vessels. The apex is directed upward and surrounds the great vessels about two inches above their origin from the base of the heart. Its base is attached to the central tendon, and part of the adjoining muscular structure of the diaphragm extends a little farther to the left than to the right side. It is separated from the sternum in front by the remains of the thymus gland above and a little loose areolar tissue below, and is covered by the margins of the lungs, especially the left. Posteriorly it forms the anterior boundary of the posterior mediastinum resting upon the descending aorta, the bronchi, esophagus, trachea, and root of the left lung. Laterally it is covered by the pleuræ, the phrenic nerve, with its accompanying vessels, descending between the two membranes on either side. There are two layers, a strong dense fibrous layer and the serous layer, which invests the surface of the heart—Cohnheim[1] observed that normally the parietal layer is always in immediate contact with the visceral.

Considering the intimate contact of the pericardium with almost all the structures of the thorax, it is not remarkable that pericarditis may be manifested in almost any portion of the thoracic viscera or even the abdominal, but still more remarkable that it may exist without giving a sign—Cohnheim pointed out that complete oblitera-

[1] Lectures in Pathology.

tion of the sac was often enough a postmortem discovery for which no symptoms during life had prepared us, and Osler confesses that it is more often discovered in the autopsy room than in the ward. In some cases this may be accounted for by lack of watchfulness on the part of the clinician, by the failure to correctly interpret the relationship of various physical signs, a too common fault, or the lack of attention to the heart when pericarditis comes late in a progressively fatal case.

Etiology. The principal change in recent years in the etiology of pericarditis is to regard all cases as of infectious origin. Osler,[2] in 1902, said that so-called idiopathic pericarditis was rare, but cases could occur, chiefly in children, in whom there was no evidence of rheumatism or any local or general disease. McFarland[3] says that there is always a focus of infection, but it is sometimes undiscoverable, and he quotes Bauer, of Munich, who states that out of 3000 autopsies occurring yearly in his city he sees only two or three cases of so-called idiopathic pericarditis. Demiéville[4] found but one case in the literature of twenty years, Virchow's case of hemorrhagic tuberculous pericarditis. Mallory[5] says that a variety of infectious agents may cause acute inflammation of the pericardial cavity. The most common are the Diplococcus pneumoniæ, the Streptococcus pyogenes, the Staphylococcus aureus, and the tubercle bacillus. They probably never lodge here primarily, but come from lesions elsewhere—thus by direct extension or through lymphatics from the lung, mediastinum, or heart, or by the blood stream from any part of the body.

Preble[6] in his series found pericarditis as a complication in pneumonia, 34 per cent; rheumatism, 28.36 per cent.; chronic diffuse nephritis, 11.20 per cent.; tuberculosis, 10 per cent.; sepsis, 4.7 per cent.; aneurysm, 2.6 per cent.; typhoid, 1.7 per cent.

Sears[7] in his report found rheumatism associated in 51 of his 100 cases, and a previous history with 40 others. Pneumonia or infection with the pneumococcus was next with 18. In 7 cases chronic nephritis was the chief cause and in 5 pleurisy—chronic rheumatism and gonorrhea are both credited with 2 cases while 1 occurred in each of the following diseases: empyema, tonsillar abscess, acute nephritis, hepatic cirrhosis, and chronic fibrous pneumonia, which was apparently not tuberculous. There were 9 cases of idiopathic pericarditis, but when we consider that some dated back as far as 1882 it is not remarkable that 9 out of 100 should be so classed.

Lamar and Meltzer[8] produced pneumonia in forty-two dogs by

[2] Practice of Medicine, 1902.
[3] Jour. Am. Med. Assn., December 7, 1901.
[4] Rev. méd. de la Suisse romande, Geneva, 1911, xxxi, 449.
[5] Principles of Pathological Histology, 1914.
[6] Jour. Am. Med. Assn., December 7, 1901.
[7] Med. and Surg. Reports, Boston City Hospital, 1897.
[8] Jour. Exper. Med., 1912, xv, No. 2.

means of intrabronchial insufflation, using pure cultures of pneumococci in suspension. They produced a lobar pneumonia in each instance. The findings in the fatal cases were similar to those in man: empyema, pericarditis, septicemia. In the fatal cases the pleural cavities contained a large quantity of bloody fibrinopurulent exudate, the pericardium was inflamed, and a septicemia existed. The exudate from the lung, pleural and pericardial cavities contained as well as the blood, large numbers of capsulated pneumococci in pairs and short chains. In their non-fatal cases it does not appear that the pericardium was involved, although much the same lung area was consolidated, but not as extensively. It would appear, therefore, that these results indicate that the pericarditis was the result of a profound septicemia.

The writer, working in the laboratory of Professor H. T. Karsner, produced pneumonia in ten dogs by the intrabronchial insufflation of pneumococcus cultures. Every effort was made to prove the organism before and after injection. One dog died on the tenth day, showing inflammatory changes in the lungs, kidney, spleen, liver, and heart. In the other nine dogs the pneumonia ran a mild course, the kidneys and liver showed moderate changes, but the hearts were normal. As far as the heart was concerned in the writer's fatal and non-fatal cases the involvement occurred only in the presence of a profound septicemia.

Torrey and Rahe[9] in their studies in canine distemper occurring in a series of ninety dogs found areas of consolidation in over 90 per cent. of lungs, while pericarditis was observed in only 5 cases, all terminating fatally. In 2 the condition was associated with pleuritis, and in 1 instance, Streptococcus pyogenes, while in the others it was sterile. The Bacillus bronchisepticus readily produces pneumonia but not pericarditis.

E. C. Rosenow[10] shows in his animal experiments with streptococci from rheumatic fever the greatest number of cases of pericardial infection corresponding with the observations of various clinicians. The interesting clinical point is that when he allows a reduction in virulence by keeping the organism in culture media there is a marked falling off in the effect of the organism on joints, myocardium and endocardium, while the pericardium does not become involved; but when the virulence is increased by animal passage the effect is less upon the joints and more on the endocardium and pericardium, especially the pericardium.

Robin and Fiessinger[11] state that gonococcus infections seldom attack the pericardium. These authors quote d'Argis, who, in 1895, collected 13 cases, and they report one case of their own. Their patient was a male, aged twenty-five years, with urethral discharge

[9] Jour. Exper. Med., January, 1913.
[10] Jour. Am. Med. Assn., November 13, 1915.
[11] Soc. méd. des. hôp. de Paris, 1912, xxxiv, 802.

and acute rheumatism complicated by signs of pericardial fluid. They aspirated at Marfan's point (base of xiphoid) and removed a fibrinous serum which did not show gonococci. The patient was treated with injections of Wright's vaccines, and made a good recovery.

The writer has not seen a case of gonorrheal pericarditis, and in the 78 Boston City Hospital autopsy cases in the last ten years there is not one recorded.

Triboulet and Harvier[12] report a case of severe typhoid in a boy, aged eleven and a half years, death being due to perforation. Acute pericarditis was unsuspected during life, but at the autopsy 90 grams of fluid were found in the pericardial sac. Cultures from the fluid gave a growth of the typhoid bacillus.

A. Pissary[13] mentions pneumonia, bronchopneumonia (especially in children), gonorrhea, scarlatina, typhoid, tuberculosis, puerperal septicemia, streptococcus infections, but places rheumatism first in etiology.

Mobécourt[14] gives an interesting case of streptococcus pericarditis in an infant; infection through the umbilical vessels at the time of birth produced a purulent peritonitis, with secondary purulent pericarditis. The purulent form, this writer thinks, is frequent in infancy because there is small defence against pyogenic organisms. This has not been the experience of Barkan and Lucas,[15] but all these authors (Bovaird[16]) agree that in small children the pneumococcus is the most frequent cause. Their articles contain exhaustive statistics on the etiology in infants and small children.

Marfan[17] says that pneumonia in children under six years and in older children and adults, acute articular rheumatism are the primary causes of pericarditis.

Of the 78 proved cases in our series, in 58 some form of acute infection was recognized before death. Pneumonia was diagnosed 28 times and acute pneumonia or pleuritis was found 49 times at autopsy. Of the 28 diagnoses of acute pneumonia, acute pericarditis was discovered before death in only 4 instances. It occurred in diphtheria 4 times, in chronic interstitial nephritis, 3; appendix abscess, 1; cerebrospinal meningitis, 2; scarlet fever, 5; general peritonitis, 3; chronic cardiac, 4; malignant endocarditis, 3; gallstones, 1; thoracic aneurysm, 3; erysipelas, arteriosclerosis, ulcerative colitis (TB) and gangrene once each. The clinical diagnosis of acute arthritis does not appear in the series, and while we have all seen acute pericarditis accompany this condition many times the mortality must be low as compared with pneumonia.

[12] Bull. Soc. méd. de hôp. de Paris, 1911.
[13] Clinique, Paris, 1913, viii, 756–759.
[14] Jour. de méd. de Paris, 1913, xxv, 383–388.
[15] Boston Med. and Surg. Jour., 1912, clxvi, 444–448.
[16] Med. and Surg. Report, Presbyterian Hospital, New York, 1912.
[17] Semaine méd., Paris, 1913, xxxiii.

The question of extension of the inflammation from adjacent organs, especially in pleuritis and pneumonia, seems still in doubt. Osler[18] believed that it could occur by extension as a serious complication in pneumonia, and he reported, in 1902, that it was present in 5 cases of 100 postmortems he made at the Montreal General Hospital. He states that in simple pleurisy it is rare.

G. A. Gibson,[19] in 1898, said that it often had its origin by extension in pleurisy and pleuropneumonia as well as in endocarditis and myocarditis, but he furthermore states that it must not be forgotten that in pneumonia the source of the pericardial infection may be through organisms conveyed by the blood, and pericarditis from pneumococci has been seen without pneumonia. Septic diseases of the mediastinal glands, mediastinal tumor (Bergmann[20]), as well as destructive processes in the lungs, may produce pericarditis by extension, while acute affections of the bones—the sternum and ribs in front and the vertebræ behind have been seen to give rise to it. In one of our cases it was due to sarcoma of the mediastinum, but it was not classed as acute pericarditis.

Preble[21] lays down rather definite statistics showing the ratio of pericarditis to the area of lung involved in pneumonia. He says that with unilobar pneumonia the chances of a pericarditis are 1 in 40; with a bilobar or trilobar, 1 in 10; with a quadrilobar, 1 in 5; with a pneumonia of the entire left lobe, 1 in 8. He feels that the danger is somewhat greater with a left than with a right-sided pneumonia. The writer has not found another author who has laid down such definite lines.

Mallory in his book states that pericarditis may occur by direct extension, and Professor Councilman makes a similar assertion in his lectures.

Sears[22] in a study of 100 cases found 34, with evidence of some previous valvular or myocardial affection, and while he says it may be a coincidence, the number is so large that it is more probable that the preëxistent lesions acted as a determining cause. Many of his cases were complicated by, or secondary to, pneumonia, pleurisy, or both, either by direct extension or from a simultaneous infection.

Brooks and Lippencott[23] found in their 150 cases of pericarditis, pleural lesions present in 136. In well over half of these cases it appears that the pleural change is the more anterior, and that the pericardial alteration occurred later, though still back of this relationship is the general disease or condition in the course of which the two membranous inflammations developed. They found a direct relationship between pericardial and pleural lesions best

[18] Practice of Medicine, 1902.
[19] Diseases of the Heart, 1898.
[20] Charite-Ann., Berlin, 1909, xxxiii, 92–101.
[21] Loc. cit.
[22] Loc. cit.
[23] Am. Jour. Med. Sc., December, 1909.

shown in the acute serofibrinous cases, in which out of a total of 67 instances, 60 showed pleural changes. In 36 of these the lesions were identical. These authors were unable to trace any direct relationship between pericardial and endocardial disease. For example, in their serofibrinous cases, 46 of which were caused by bacteremia of some variety, only 10 showed acute endocardial changes; 7 of these were unquestionably rheumatic and bore no other relation to the pericarditis than that both had probably a common etiology.

Sinnhuber,[24] believes that acute articular rheumatism is the foremost cause of pericarditis, then pneumonia, tuberculosis, scarlet fever, influenza, typhus abdominalis, recurring fever, cerebrospinal meningitis, malaria, erysipelas, osteomyelitis, pyemia and sepsis, gonorrhea, scurvy, leukemia, and certain forms of cirrhosis of the liver. He also states that it can arise from diseases of the neighboring organs, endocarditis, myocarditis, diseases of the pleura, especially on the left side, perforation of the esophagus from a foreign body, caries of the sternum and ribs, and as a sequel of aneurysm.

In our series cultures were not always made, but in the 78 cases the streptococcus was recovered 19 times, the pneumococcus 17 times and staphylococcus 8. In one of the cases of cerebrospinal meningitis the meningococcus was recovered from the brain and pericardium, and in the other case the heart's blood showed streptococci, and the pericardium, staphylococci.

Symptoms. The symptoms of pericarditis are so varied and the onset so insidious in some cases that Osler and almost every other author has been led to say that many cases run their entire course without recognition. When it comes on very gradually, or is the only manifestation of an obscure focus, or is well established when the patient comes under observation, detection is sometimes most difficult if not impossible. The importance then of a thorough physical examination of the heart and lungs at the first visit, with subsequent daily examination augmented by careful notes and charts, is obvious. It is well to mark out the percussion lines on the chest and to test them daily for any change. The intensity of all the heart sounds, their relation to one another, and the character of murmurs should be carefully noted.

Pain is an important subjective sign and one which a good many practitioners expect to find. Pleurisy is almost immediately painful, and so it is thought that pericarditis will be; but one should not expect to have the patient complain of pain as he does in pleuritis.

A. McPhedran[25] says that pain is generally present, and quotes Sibson, who found it in 70 per cent. of his cases. L. V. Schrötter[26]

[24] Die Erkrankungen des Herzbeutels und ihre Behandlung, Berlin, 1911.
[25] Osler's Modern Medicine, 1908. [26] Nothnagel's Practice.

states that the greater number of cases occur without pain. James Mackenzie[27] calls attention to the absence of pain in a good many cases. Poynton[28] says it may occur with little discomfort and no pain. Pain was present in 65 cases in the series of 100 reported by Sears, and when absent its place was taken by a sense of oppression in the chest.

Babcock[29] found pain in the majority of his cases, or if not, a sense of distress.

It has seemed to the writer that a good many patients with acute disease of the heart, while they do not have actual pain in the heart, still when one asks if ice over the precordia makes them feel more comfortable, they generally say that they prefer to have the ice kept on.

Blumer[30] states that pericarditis is often almost without pain.

Billings[31] does not mention pain in his text, and in only one case history.

In the protocols of the 78 cases in our series, pain was not a striking feature, and was observed 26 times—in 17 of the 26 cases there was either acute pneumonia or disease of the pleura, in 2 others chronic disease of the myocardium, and in 1 aneurysm of the arch of the aorta, leaving but 6 cases out of the 26 with pain directly over the precordia.

In the 2 cases of purulent pericarditis with operation (one recovered, the other died without autopsy) pain was not observed at any time.

It has been the writer's experience repeatedly in cases of slight dry and serous pericarditis lasting a few days to note the absence of pain, although in this study no conclusions from figures can be given.

It must be remembered that many of the patients in our series were seriously ill at the time of entrance to the hospital, and their general distress was so great that they may not have noticed pericardial pain.

The cause of pain is difficult to determine. The pericardium, like other membranes, the peritoneum and pleura, are insensitive when normal, but if inflamed, pain is produced. Special work seems necessary on this subject.

Poirier[32] says it is very probable that the left pneumogastric and the nerves of the cardiac plexus give off also several nerve fibers to the fibrous layer.

The skin over the precordium is sometimes tender because of the connection between the upper intercostal nerves and the ganglia and nerves of the cardiac plexus (Piersol[33]).

[27] Diseases of the Heart, 1908. [28] Pediatrics, New York, 1910, xxii, 353–363.
[29] Diseases of the Heart and Arterial System, 1905.
[30] Jour. Am. Med. Assn., July 18, 1914.
[31] Ibid., December 7, 1901.
[32] Anatomy. [33] Anatomy.

Krehl[34] quotes Goldscheider,[35] who denies the existence of special nerves of pain. He continues with the statement that every sensation produces at the same time a more or less definite impression of the place whence the sensation has come. In the case of the eyes and skin the localization is very accurate; in the case of the mucous membranes near the outside of the body it is somewhat less accurate; in the case of the mucous membranes and the organs within the body it is inaccurate and entirely unreliable. Howell[36] also makes this last statement.

Albutt[37] states that there are cases in which the pain is like that of angina pectoris, and refers to several observers, Sibson, Byron Bramwell and others.

In studying the subjective symptoms of pain and a feeling of distress in the precordia or chest in pericarditis, it seems to me that it makes a great difference whether one builds his statistics of pain on clinical or autopsy observations. When one considers that only about 50 per cent. of the cases are recognized, and of that number about one-half have precordial pain, it makes the pain a small factor.

Pericardial Friction. In a pericarditis which remains dry or rather has but a moderate increase in fluid the sole physical sign is the to-and-fro friction rub. It is generally heard, if only for a few hours, in almost every case of plastic pericarditis.

Billings[38] says it is present in every case at some time in its course, and by systematic examination it will be found.

McPhedran[39] thinks there are many cases in which it is not found, "but once distinctly heard it can scarcely be confounded with anything else." The writer feels hardly able to make such a sweeping statement. Meeting a considerable number of students of all ages every year in the Graduate School of Medicine of Harvard University, it is uncommon to have a student recognize a pericardial friction rub. Three years ago a very able practitioner from Vermont told me that he had been in practice thirty years and had never heard a pericardial rub until he came to our clinic. This is not surprising when one considers that acute pericarditis is not such a very common complication, having been diagnosed clinically but 100 times in 34,467 medical patients treated in the wards of the Boston City Hospital during the last ten years by physicians giving a good deal of time and thought to diseases of the chest. Acute pericarditis has been found 78 times in 1553 autopsies during the same period.

Many writers speak of the pericardial changes beginning at the point where the membrane is in contact with the great vessels,

[34] Clinical Pathology, 1909.
[35] Ueber den Schmerz, Berlin, 1894.
[36] Text-book of Physiology, 1913.
[37] Diseases of the Arteries, 1915.
[38] Loc. cit.
[39] Loc. cit.

because the infecting agent is carried to the sac by the blood, and at that point the blood supply is richer.

Rosenow[40] found in the pericarditis of animals that hemorrhages usually surrounded a relatively large artery. In some of the sections the artery was the seat of thrombosis, or accumulation of leukocytes along the intima in the area of the hemorrhages. Some of the leukocytes contained organisms, and in one instance typical organisms were found directly in the wall of an artery which showed mural implantation of leukocytes adjacent to an area of hemorrhage in which exactly similar organisms were found in small numbers.

Mallory[41] says that it may occur anywhere in the pericardial sac. In one case of the series of 78 autopsies of acute pericarditis the inflammation was found about the great vessels, but more often it involved the entire sac. In animals the focus can be more readily studied while the human subject often does not die until the entire sac is involved.

In the experiments of Walker and Christian[42] in the production of pericarditis by the injection of spartein sulphate and adrenalin chloride, the inflammation was usually adjacent to the left ventricle.

The chief difficulty seems to be in distinguishing the rub from a valve murmur. The rub even when faint will generally have a jerky, grinding, or leathery quality. Because of the more active movements of systole it may seem to be wholly a systolic sound, but by listening carefully a sound of similar quality, sometimes very faint, will be heard in diastole. The rub may be mistaken for a valve murmur even by the most experienced. Three years ago, when looking for a case of aortic stenosis to show the students, I was told by the house physician of a colleague, distinguished as a specialist in circulatory diseases, that they had a case in Ward M. The patient, a man, aged twenty-seven years, was convalescent from an acute multiple arthritis. He looked well and said that he was absolutely free of his discomforts. On listening to his heart he was found to have over the second interspace to the right of the sternum a rough, grating murmur, systolic in time. On listening carefully, however, a similar murmur, very faint, was heard in diastole. There were absolutely no cardiac or circulatory signs indicating aortic stenosis or regurgitation. In the absence of these confirmatory signs of valvular disease, outside of the precordia and taking into account the history of recent rheumatism, it seemed more probable that he had a pericardial friction rub. Two days later the rough sound, with its fainter diastolic, was heard over the third interspace to the left of the sternum, the following day over the fourth, and by the fifth day it was barely audible just above the cardiac impulse, and then disappeared. Within two months a consultation was held at the hospital to decide whether a patient

[40] Jour. Infect. Dis., May 16, 1915.
[41] Loc. cit.
[42] Tr. Assn. Am. Phys., 1910.

had double aortic disease or pericarditis. The same considerations decided in favor of pericarditis.

The rub often moves from day to day, and is sometimes made more intense by pressure with the stethoscope. When the rub disappears it may mean that the plastic pericarditis is quieting down or fluid is accumulating.

Fluid. In many cases, the majority in fact, a little increase in fluid occurs and then quiets down. It is not recognized clinically, as it gives no physical signs because the sac is distensible and the added pressure causes no embarrassment to the heart or circulation.

Poynton[43] says that paracentesis is rarely needed in childhood, thereby indicating the frequency of spontaneous absorption.

The cardinal points which have always been taught are increase in the cardiohepatic angle, increasing faintness (distant) of the cardiac sounds, the disappearance of the cardiac impulse, and the pulsus paradoxus.

Percussion should be performed daily or oftener marking out carefully the cardiac borders. The angle of cardiohepatic dulness will be found to increase with increasing fluid. James Mackenzie[44] says that the dulness will also reach up to and above the second rib and the area mapped out will have a somewhat pear-shape appearance. This shape has been seen several times by the writer, and in a roentgenogram the enlarged area looks like a paper bag filled with water and set down upon a table. In comparing these roentgenograms with those from dilated hearts the line in the latter is almost always a curve inward as it approaches the liver. If the increase is due to enlarged liver it can generally be distinguished by a study of other pericardial signs of effusion, such as a faintness of heart sounds and disappearance of the cardiac impulse.

Emphysema may mask the heart sounds so that there may be poor sounds with a good pulse, as is often the case in pericardial effusion. When there is a left pleural effusion the heart may be pushed to the right and the border between the pleura and the pericardium will be lost. Aspiration of the pleural fluid should reduce the cardiohepatic angle, and if it does not, after the heart has had time to return to its normal position, pericardial fluid should be suspected (Cabot[45]).

Shifting dulness has not been helpful to the writer. The fluid is generally under such tension between the myocardium and the fibrous parietal pericardium that it is not clear how it could shift. When the fluid is posterior the heart may be pushed forward and there may be no diminution in the cardiac impulse. In a case seen in consultation the increasing cardiohepatic angle and signs of distress raised the question of fluid. A roentgenogram showed the characteristic pear-shaped enlargement; still, we hesitated to aspirate

[43] Loc. cit.
[44] Diseases of the Heart, 1914.
[45] Physical Diagnosis.

because of the very distinct cardiac impulse. A second roentgenogram was taken, showing an increase in size, and upon aspiration about 150 c.c. of bloody serum were removed, with considerable relief to the patient. In these cases almost all authors, Billings,[46] Babcock,[47] J. Mackenzie,[48] Cabot,[49] Musser,[50] Parkinson,[51] call attention to the small area of dulness in the left back just inside the angle of the scapula, described by Ewart, and produced by mechanical atelectasis of the compressed lung.

Moog[52] adds one case to a report of four others of pericardial effusion punctured in the rear. He tapped the pericardium through the fifth interspace in front and evacuated 130 c.c. of hemorrhagic fluid; two days later he evacuated 90 c.c. in the same way. The symptoms from compression of the lung soon returned, but two punctures at different points brought no fluid. Then he introduced the needle in the rear in the eighth space and obtained 600 c.c. of the effusion, the same amount the next day; and five days later 400 c.c. Air got in during the later puncture, and pneumothorax developed with some effusion, but this gradually disappeared with all the other symptoms. The patient made a good recovery.

Pauly[53] calls attention to the signs in the back.

Curschmann[54] reports 3 cases of successful paracentisis in the back at the eighth interspace.

Mackenzie[55] reports having tapped a purulent pericardial effusion from the back in mistake for an empyema, his mistake arising from not having ascertained the position of the heart's movements. He says that had the case been one of pleural effusion he would have found the heart beating to the right of the sternum, but the whole left chest was dull, so that the idea of it being a pericardial effusion did not occur to him. One of my hospital colleagues told me that he made a similar mistake two or three years ago.

R. C. Larrabee and the writer tapped a boy, aged ten years, just in front of the left midaxillary line, removing several ounces of bloody fluid. The almost immediate cessation of cardiac distress convinced us that we had put the needle into the pericardial instead of the pleural cavity.

The pulsus paradoxus, which is small and feeble during inspiration, was formerly considered as important, but it occurs in other conditions and even in the normal subject.

Musser,[56] Cabot,[57] West,[58] and many others mention it, but do not regard it as important. In one case in the writer's series it was noted.

[46] Loc. cit. [47] Loc. cit.
[48] Loc. cit. [49] Loc. cit.
[50] Medical Diagnisis, 1913.
[51] Clin, Jour., London, 1912, xl, 45.
[52] Therap. Monat., Berlin, June, 1914.
[53] Rev. de méd., Paris, 1911, xxxi.
[54] Therap. Monat., Berlin, 1912, xxvi.
[55] Loc. cit.
[56] Loc. cit.
[57] Loc. cit.
[58] Lancet, London, 1910, i, 560–564.

Taussig[59] says that ordinarily the dicrotic wave in the radial sphygmogram does not vary in size with the phase of respiration. In pericarditis, however, it becomes more or less exaggerated, sometimes greatly so, during inspiration. He studied 5 cases, making this observation in all.

The writer has not had experience with the following signs:

Wynter[60] believes that absence of the abdominal respiratory movement is an indication of pericarditis. He reports 2 cases in which the remarkable stillness of the abdomen led to a diagnosis of acute abdominal lesions, pericarditis being discovered later. It is a valuable sign, he thinks, as it may precede and outlast other indications. The inflammation of the pericardium may cause reflex inhibition of abdominal movement some days before the appearance of the ordinary clinical signs. It is more apparent with a fibrinous exudate. He reports 10 other cases in which he found this sign.

When we remember that the base of the pericardial sac rests upon the diaphragm it is quite as possible to give abdominal symptoms as in the well-known instances of inflammations of the pleura and lung.

In the only cases in our series in which abdominal pain was noted there was definite disease of the abdomen.

Cobb[61] has reported a case of acute serohemorrhagic pericarditis in a boy, aged eleven years. He had never been sick until ten days before Cobb saw him, when he had an acute coryza, with the exception that he complained of a little pain at the apex of the left lung on deep inspiration. His physician found nothing but a few slight friction rubs, which disappeared within twenty-four hours. The temperature did not go above 100.5° F., and became normal at the end of the third day. Three days after apparent recovery and five days before Cobb saw him he ate heartily of apples and ice-cream, was seized with a sudden attack of abdominal pain, which made him cry out and writhe on the floor. He vomited several times in this attack; the temperature was 100° F., but nothing could be found on physical examination. He recovered in a few hours and was apparently as well as ever. Three days later he had some nausea and vomiting, and complained of abdominal pain. This was followed by a day of comfort, when he again had nausea, vomiting, epigastric pain, and pain in the right hypochondrium well down in the flank. He was apparently very sick, with a rapid and irregular pulse. In the epigastrium and right and left hypochondrium there was exquisite tenderness. After careful examination of the chest, nothing abnormal was found except the respiration in the left back was somewhat shallow, apparently due to the tenseness in which

[59] Jour. Am. Med. Assn., June 13, 1914.
[60] Clin. Jour., London, 1911–12, xxxix, 218.
[61] Ann. Surg., October, 1912, lxi.

the abdominal muscles were held because of the pain. The heart was normal in size and situation. Upon opening the abdomen in the median line nothing was found except a very large and congested liver. At the autopsy the pericardium was found to be 5 mm. thick and contained a considerable amount of bloody fluid with soft fibrin, free and attached. Cultures were not reported.

The writer thinks that the shallow breathing in the left back may have been due to the pericardial pressure—Ewart's sign; the congested liver, to pressure about the great veins within the sac. The heart valves were normal.

I was once asked to see a physician's wife who had been taken to a private hospital with a diagnosis of appendicitis. Certain features in the case prompted the surgeon to ask for a medical consultation. The history was that she became easily tired and a little short of breath on exertion. She had had three attacks of abdominal pain, which seemed to bear a relation to her menstruation. On physical examination a marked mitral stenosis was found and an enlarged and tender liver. By resting the heart the liver reduced in size and the attacks of pain ceased.

Calvert[62] believes that in pericarditis with effusion the right lobe of the liver is low, varying in its position from the 5th space to the 6th rib; in dilatation of the heart the right lobe of the liver is high from the 4th to the 5th rib. He reports 2 cases of pericarditis to confirm this.

The writer has not met with this sign nor has he found mention of it elsewhere, but it seems extremely doubtful if it would give much help. Turrettini[63] studied a sign noted by Josserand,[64] and Mouriquand and Roubier[65] of impending pericarditis or endocarditis. Turrettini observed this sign, "Éclat clangoreaux disastolique au foyer pulmonaire" in 2 cases, a sudden and violent clanging diastolic sound in the pulmonary area. The pulmonary second sound was very pronounced and the vibration could be felt by the hand. The second aortic sound was perceptible, but less marked, a friction rub developed soon after. His cases are not very helpful, as one patient had chronic nephritis with hypertrophy and dilatation and the fibrinous pericarditis developed slowly while the patient was under treatment, and the other was similar without autopsy. In two other cases of pericarditis from the spread of a pleural process this peculiar clang was never heard. He believes the sound to be important because it enables one to recognize incipient pericarditis, and by instituting treatment in time to possibly ward it off. The writer does not find in the literature any other observers who have made use of this sign. In chronic nephritis the diastolic

[62] Arch. Int. Med., 1909, iii, 92; Jour. Am. Med. Assn., August 27, 1910.
[63] Rev. méd. de la Suisse romande, Geneva, 1913, xxxiii.
[64] Lyon méd., November 17, 1907.
[65] Ibid., September 1, 1907.

second sound is often sharp and ringing, until the systolic blood-pressure falls and cardiac compensation fails.

The knee-chest position has been considered by Rieux[66] to be of diagnostic value. The writer has never seen a case of pericarditis with this sign. In diseases of the chest patients assume the most comfortable attitude for breathing.

The diagnosis in dry pericarditis rests solely upon the to-and-fro friction rub. The fluid which usually follows may be so slightly in excess of the normal as to escape detection and with the disappearance of the rub nothing further may be found, or there may be a gradual or rapid change in the area, the obliteration of the cardiohepatic angle, dulness extending to and above the second rib; the disappearance of the cardiac impulse; the faintness of the cardiac sounds; increasing cardiac distress sometimes out of proportion to the cardiac findings; cyanosis and signs of embarrassed circulation. In a man, aged thirty-two years, who had been ill two weeks with pneumonia, was getting better and then began to grow worse, the right border of the heart was 7.5 cm. from midsternum, the left border 14 cm. The apex beat was indistinctly felt in the 5th space within the nipple line. The cardiohepatic angle was distinctly obtuse. The striking point was the difficulty of hearing anything in the way of heart sounds. The abdomen was practically negative, and there was no sign (Ewart) in the back. Dr. G. G. Sears, who saw this patient shortly after he entered the hospital, immediately made a diagnosis of pericarditis with effusion, based on the rapidity of respiration, hoarseness of voice, size of cardiac dulness, and lack of heart sound with a fairly good pulse. The roentgen-ray confirmed the diagnosis. A needle inserted in the fifth space at the left outer border of cardiac dulness gave 20 c.c. of seropurulent fluid. At operation about 2 quarts of pus were removed. The patient seemed relieved, but died a few hours later.

Sears[67] has said that unresolved pneumonia is a pathological myth. If the temperature keeps up and the signs persist after due course of time, something is amiss. If we can exclude complications outside the lungs as a cause of fever, *e. g.*, otitis media, pericarditis or endocarditis, one arrives at a diagnosis by exclusion of either pulmonary abscess or empyema, and of these the latter is vastly more common. These words might also be used in discussing pericarditis; sometimes the pleural cavity is aspirated first in doubtful cases (Ortner[68]); Harrigan[69] thus excluding paracentesis of the pericardium or proving its necessity.

We will speak of paracentesis as a diagnostic as well as a therapeutic procedure. It is necessary in cases progressing unfavorably

[66] Paris méd., 1912–13, xi, 185–191.
[67] Boston Med. and Surg. Jour., November 25, 1915.
[68] Deutsch. med. Wchnschr., Leipzig., 1910, xxxvi.
[69] Ann. Surg., lvii, 1913.

to determine the plan of treatment. The point of puncture is decided by the physical signs and the roentgen-ray.

Pendlebury[70] says the spot chosen for introduction of the aspirating needle, of not less than one-tenth in diameter, is in the 5th left interspace, one inch from the margin of the sternum. By choosing this spot injury to the pleura and danger of wounding the internal mammary artery will be avoided. The most careful aseptic precautions must be observed, and he advises incising the skin before putting in the needle. He urges careful attention to the first few drops of fluid to avoid injury to the heart. These directions are also given by Friedrich Pels-Leusden,[71] who adds that we may in the above method occasionally prick the heart, and furthermore says that we may go in the mammary line in the 5th space in which the mammary artery and the heart are not imperilled, but where we must necessarily go through the pleura. Curschmann advises puncture always far outside at the limit of dulness and to go without fear through the pleural cavity, even if the latter is matted down by adhesions, so as to be sure not to injure the heart.

Ogle[72] advises introduction of the needle slowly and steadily, and as soon as it is through the skin the aspirator should be connected and the glass index watched for the first indication of fluid.

The writer has had his chief experience with the above method. Blechmann[73] in an exhaustive article discusses the various methods of exploratory puncture. The one already described by Pendlebury (Dieulafoy[74]), the left parasternal (Delorme and Mignon[75]), the right parasternal (Rotch[76]), and Marfan's[77] epigastric xiphoid route.

As Curschmann says, no definite rule can be laid down in any case. We must be guided by the area of dulness, the findings by exploratory puncture and the roentgen-ray.

In our other case of purulent pericarditis following pneumonia the right border of cardiac dulness extended until within 2 cm. of the right nipple, and exploratory puncture was made in the 4th space to the right of the sternal margin and the operation followed the same line, the 4th and 5th costal cartilages being resected. This patient made a good recovery and the discharge ceased in three weeks.

The chief worry of the novice in exploratory puncture is the fear of wounding the heart. Sears[78] says: "That the danger arising from wounding the heart is theoretical rather than real received

[70] Latham and English, System of Treatment, 1915.
[71] Handbook of Surgical Operations.
[72] Latham and English, 1915.
[73] Semaine méd., 1913, xxxiii.
[74] Traité de l'aspir. des liquides morbides, Paris, 1873.
[75] Rev. de Chir., 1895, 797–787.
[76] Boston Med. and Surg. Jour., 1878, xcix.
[77] Semaine méd., Paris, 1913, xxxiii, 469–476.
[78] Boston City Hospital, Med. and Surg. Report.

another illustration in one of these cases when the needle thrust into the 6th interspace just to the right of the sternum entered a solid body which pulsated and caused it to describe an arc of one and a quarter inches with each beat. No harm results."

Ewart considers the removal of blood sometimes most beneficial, and Sharkey[79] reported a case in which the blood came through the trocar in jets. It did the boy a great amount of good.

Byron Bramwell[80] reports a case of continued hemorrhage into the pericardium from puncture of the ventricle.

In rabbits, blood is removed from the ventricle for therapeutic purposes without doing the rabbit any harm.

Cushing and Branch[81] in their report on work done in the production of chronic valvular lesions in dogs found that in spite of the most rigid asepsis neither the pericardium nor the pleura withstand operative measures with anything like the resistance which the peritoneum exhibits in the face of similar manipulations. A considerable number of the animals which recovered and were subsequently sacrificed showed evidences of a slight degree of infection. They add, however, that no one who has not had experience with operations on animals can have any idea of the amount of handling the heart will stand without injury.

In Harrigan's[82] case of temporary arrest of the heart beats following incision of the pericardium for suppurative pericarditis, the heart was seen lying still, but it began to beat again as soon as gauze was introduced into the sac. This was a feeble child much exhausted by a long-standing infection, but recovered from the immediate effects of the operation.

Sears calls attention to the fact that the heart is more apt to show signs of embarrassment with arrhythmia and enfeeblement of the pulse when the effusion begins to form, later when the sac begins to distend the circulatory signs are less urgent. In accord with this are the findings of Heitler,[83] who electrically and mechanically stimulated the visceral pericardium, thereby considerably disturbing the cardiac rhythm even after section of the cardiac nerves. He found the left ventricle excitable, especially over the upper third; the right ventricle is not markedly excitable except close to the sulcus, while the apex is variable.

Mackenzie[84] has never found any serious embarrassment from extensive pericardial effusion. The pericardium normally is an inelastic bag, but with inflammation it becomes distensible.

Chatin[85] found that the amount of fluid which could be forced into a normal pericardium was 700 c.c., but in inflammation very

[79] Lancet, December 6, 1902.
[80] Clinical Studies.
[81] Jour. Med. Research, February, 1908.
[82] Loc. cit.
[83] Wiener klin. Wchnschr., 1898, No. 3.
[84] Loc. cit.
[85] Rev. de méd., June 10, 1900.

large amounts may accumulate. Kay[86] reports a case in which at autopsy 3500 to 4000 c.c. were found.

When the fluid is in large amount the pressure symptoms on the auricles and great veins may become marked, and death may result. Another danger (M'Phedran[87]) is the interference by pressure with the coronary blood supply, this favoring degenerative changes in the structure of the heart.

TREATMENT. The question of injection into the pericardial sac after removal of the fluid is unsettled. Few observers can see any advantage, and almost all regard attempts at local medication to be harmful. Washing out the sac even with normal salt solution is without supporters. The object of any form of local treatment is to prevent adherent pericardium.

Wenckeback[88] obtained good results by introduction of air. He removed the fluid and put in one-half the volume of air. He suggests using nitrogen or oxygen.

Wilbur[89] quotes McPhedran, who advises in pyopericardium the injection of a 2 per cent. liquor formaldehyde in glycerin, as is sometimes used in empyema.

Rehn[90] injected dogs' hearts with tincture of iodin and with aleuronat, produced synechia, and then checked adhesions by injections of sesame oil. Wilbur suggests the use of some oil, such as liquid petroleum.

In pyopericardium, free incision with drainage is indicated as in empyema. Manual removal of fibrin is sometimes necessary.

Medical treatment is thoroughly discussed in several good text-books. Ice is of value and is used in every case in the Boston City Hospital whether there is pain or not. I always ask the patient if it gives him comfort, and he generally replies in the affirmative. Be sure that the ice-bag is not too heavy—it is sometimes an added burden to a laboring chest.

Rubino[91] found that he was able to produce pericarditis in animals by the intravenous injection of cultures of pyogenic cocci only when ice was simultaneously applied to the chest. On this ground, ice has been objected to as a therapeutic measure, but Rubino probably severely chilled the animals and lowered their resistance.

The treatment by drugs is nearly useless, but whatever is done is generally indicated by the infective process.

In rheumatism the salicylates are of undoubted value. It has been said that they sometimes depress the heart, but it is more probable that the depression comes from the toxemia.

[86] Penna. Med. Jour., 1911–12, xv.
[87] Loc. cit.
[88] Ztschr. f. klin. Med., Berlin, 1910, lxxi.
[89] Jour. Am. Med. Assn., July 25, 1914.
[90] Arch. f. klin. Surg., Berlin, 1913, cii.
[91] Arch. Ital. de Biol., 1892.

Pericarditis occurring before the crisis of pneumonia is apt to mean an overwhelming toxemia, and the prognosis is very grave. Later, after the patient has begun to improve, the effusion is often purulent, and the treatment has been discussed.

The diet should be light and easily assimilable, as in cardiac and acute infections.

Absolute rest in bed until the signs of pericarditis have ceased and the heart has fully regained its tone is of vital importance.

Conclusions. The conclusions from the literature and the series of cases are:

1. Acute pericarditis is a secondary affection. Several other lesions were found in every case in the 78 autopsies.

2. The extension from adjacent structures is probably uncommon, the vast majority of cases occurring from infection of the sac through the blood stream.

3. Pain in the precordial area is not as common as is supposed. A good many mild cases pass unnoticed because there is neither pain nor distress. In rheumatism with an acute heart the pain and arrhythmia may be noticeable at first, but later when all structures of the heart are involved the picture is one of general cardiac and circulatory embarrassment. Pain is so much more common in pleuritis, and pneumonia plays such a factor in pericarditis, that it is often difficult to separate the two.

4. The difficulty in diagnosis is illustrated by the fact that acute pericarditis was recognized clinically only 100 times in 34,467 cases and 12 times in 78 autopsies at the Boston City Hospital. Pneumonia is the chief agent in the production of purulent and of fatal pericarditis. Rheumatism may cause a greater number of cases of all types, but the figures are open to doubt, as they include all grades of severity, and many can be studied from their inception, while in a rapidly progressing infection like pneumonia the changes in the heart may be masked by adjacent physical signs and the cardiac and respiratory distress of the patient. Rheumatic pericarditis should always be thought of, especially in young adults, when the signs of cardiac failure are out of proportion to the other cardiac physical findings. Pneumococcus pericarditis or myocarditis, or both, should be considered, especially in young or middle-aged adults, when the heart shows failure of compensation before the crisis or after it when there is fever and delayed convalescence.

5. The prognosis in acute pericarditis following acute arthritis is generally favorable to life; the extent of damage to the subsequent function of the heart cannot be determined, of course, immediately. In the clinical protocols of this series, acute arthritis was not found once. Pneumococcus pericarditis is grave at any stage. Tuberculous pericarditis is not common, and is usually a late involvement in an advanced case.

6. In mild cases of fibrinous pericarditis or of moderate effusion,

especially when an accompaniment of acute arthritis, treatment of the infection and local applications to the precordia will often suffice. When the progress is unsatisfactory, the physical signs increasing, and the diagnosis doubtful, paracentesis is imperative.

7. Frequent examinations during the infection and for some time after are very important. A thorough search for and the eradication of foci should be conducted in every case.

The writer wishes to thank Dr. Sears, Dr. Councilman, and Dr. Mallory for many valuable suggestions, and the members of the Visiting Staff of the Boston City Hospital for the privilege of referring to the records of their cases.

A TREATMENT OF GASTRIC ULCER BASED UPON ESTABLISHED CLINICAL, HISTOPATHOLOGICAL AND PHYSIOLOGICAL FACTS.[1]

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Even a casual acquaintance with the literature of peptic ulcer demonstrates that treatment of the affection has been largely empirical. Various types of therapy appear to have obtained a vogue because their application either relieved symptoms or appeared to prevent a fatal issue. Success of a mode of treatment has been judged mainly from its effect upon the immediate condition and not with respect to the ultimate outcome of the affection. It is most unusual to observe statistics of hospitals or private practices that indicate the status of patients treated after intervals of five to twenty-five years. Hospital records generally state that a peptic ulcer patient has been discharged either "cured," "improved," "not improved," or has "died." With exception of the fatal cases, facts are usually not available regarding the future course of the ailment, inasmuch as these patients frequently seek the advice of another physician should their disability return after a long and expensive course of treatment at the hands of a former physician. It is also of interest to observe that of a half-dozen experts non-surgically treating peptic ulcer by radically different regimes the percentages of cure show a range of but five to ten points. We have also been impressed by the fact that at the most competent hands, certain ulcers resisted all types of treatment alike. It has seemed to us that unsatisfactory as the treatment of peptic ulcer might be,

[1] Read at the Annual Meeting of the American Gastro-enterological Association, Washington, D. C., May 8 and 9, 1916.

it were possible to devise a type of management that at least had the merit of resting upon certain basic principles. It likewise appears to us that methods of therapy are dependent upon information that has been returned by recent histological, physiological, and clinical investigations.

I. The Problem.

1. *Clinical.* Peptic ulcer is a disease which may or may not exhibit symptoms or signs. It is an ailment which, in its uncomplicated form, may be so closely mimicked clinically by nonulcerous dyspepsias as to deceive the most experienced diagnostician. Until complications occur it is a disease characterized in 84 per cent. of instances by a peculiar "periodicity," and which often manifests itself by recovery and relapse frequently wholly independent of type or duration of treatment. It is associated with a form of gastric malfunction whose cessation does not generally indicate eradication of its exciting causes. It is a disease about which little prophecy respecting its extent or its future course can be made from its clinical symptomatology. Acuteness of symptoms does not wholly indicate the histopathological changes existing at the diseased focus—for acute manifestations histologically can be engrafted upon chronic inflammatory tissue pathologically. The most serious clinical outcome may frequently follow upon spontaneous or so-called therapeutic cure with the subsidence of the initial dyspeptic upset. Stenoses, gastric malformation, involvement of extragastric viscera, fatal hemorrhage, or malignant transformation may occur with comparatively slight clinical manifestation or certainly with relatively little change in the patient's complaints. Peptic ulcer is an ailment entirely indistinguishable clinically from the early appearance of gastric cancer, syphilis, or tuberculosis. It is a disease which but rarely occurs in individuals not already affected with other clinical abnormalities—infections about the head, throat, and neck; abdominal disease, *i. e.*, inflammatory changes in the appendix, gall-bladder, perigastric lymph nodes, pelvic structures, etc.; disturbances in the circulatory, eliminative, nervous, or lymphatic systems; and malfunctions of that group of glands concerned with food digestion and assimilation. Finally, it is an ailment of almost universal distribution, and one capable of producing such disturbance of the physical and mental health as to demand relief.

2. *Nature of Peptic Ulcer as Shown by Experimentation.* Before discussing the possibility of curing an ailment, it would appear quite essential that one be adequately informed regarding the character of the existing malfunction. That such inquiry is especially warranted with respect, gastric ulcer is indicated by the observation that scarcely a year has passed since the classic monograph of Virchow that has not seen a new attempt at explaining

the cause of ulcer of the stomach. Usually, closely attached to this experimental or clinical investigation there has also been cited a supposedly new method of healing the affection. That the majority of these contributions have proved unsatisfactory is clearly indicated by a recent elaboration of the "corrosion theory" of the origin of peptic ulcer, a theory pronounced inadequate forty years ago by von Leube, and often since revived.

Study of the affection demonstrates that a narrow conception of gastric ulcer is impossible. Competent observers have experimentally produced gastric ulcer by a wide variety of methods. It has been shown that gastric ulcers differing slightly in type histologically can be caused equally as readily from the systemic as from the local intragastric point of attack. Some of the more familiar causative agents are: (*a*) *Bacteria* (pneumonococci by Dieulafoy; staphylococci by Widal and Meslay; Staphylococcus aureus by Letulle; B. pyocyaneus by Charrin and Ruffer; B. dysenterii by Chantemesse and Widal; lactic acid bacillus and B. coli by Rodet and Zaidmann; streptococcus by Rosenow); (*b*) *Bacterial toxins* (pyemias by Lebert and by Cohn; diphtheria toxin by Enriguez and Hallion and Rosenau and Anderson); (*c*) *cutaneous burns* (Welty, Ponfick, Silberman, Parascandolo); (*d*) *poisons of metabolic origin* (Bolton's "gastrotoxin" injected intraperitoneally or subcutaneously); (*e*) *extrinsic poisons* (mercury salts, arsenious acid, cantharidine, vegetable alkaloids, pilocarpin and atropin, copper sulphate); (*f*) *poisons introduced into the stomach* (corrosives, caustics); (*g*) *alterations in the stomach's circulation* (vascular blocking, adrenalectomy, thrombi, emboli, arteriosclerosis or nervous inhibition, external pressure); (*h*) *artificial pyloric spasm or stenoses* (Hamburger and Friedman); (*i*) mechanical trauma. Whatever may be the experimental mode of production, the types of ulcer resulting appear to vary but slightly. The lesions produced are essentially similar. There is inflammatory edema, loss of surface epithelium, hemorrhage, necrosis, glandular destruction, and frequently infection. In the healing of ulcers, irrespective of the way they may have been produced, the basic features consist in development of protective connective tissue by hyperplasia, with resultant scar.

The experiments of Bolton and of Rosenow are particularly interesting. The latter investigator has recently revived the bacterial theory of ulcer causation. By intravenous injections of streptococci usually obtained from throat and mouth lesions which have undergone a certain mutation culturally, Rosenow has succeeded in producing both acute and chronic gastric ulcer. From these ulcers he has been able to recover organisms, morphologically and culturally, similar to those with which, experimentally, he produced the lesions. He also has been able to demonstrate the inter-relationship of infections of the appendix, gall-bladder and

pancreas, and peptic ulcer with regard the streptococcus. He has shown the possibilities of organisms infecting the mouth, throat, or head sinuses gaining access to the general circulation and contributing to intra-abdominal pathology, or, by direct infection of the alimentary tract producing or aggravating ulceration. While Boetcher, Letulle, Dieulafoy and others many years ago advanced similar experimental proof, yet Rosenow, by tissue culture, has emphasized the significance of bacterial action in association with local or disseminated foci of chronic infection. However, as the definite causative factor of gastric ulcer, and particularly with respect its being *only cause*, Rosenow's bacterial proof cannot be wholly accepted. The ulcers which he has produced are not in any way dissimilar from those produced by other investigators using organisms other than the streptococcus or those ulcers caused by a wide variety of non-bacteriological agents. Rosenow has failed to show that the streptococci recoverable from injured mucosæ in the alimentary tracts of his experimental animals have not been secondarily deposited there as a consequence of some preceding, local, cellular fault. Control experiments using organisms other than streptococci are likewise lacking.

Antedating Rosenow's observations, and apparently being more basic in principle etiologically, are those of Bolton. This investigator has shown by an extensive series of experiments that *non-bacterial* tissue injections quite uniformly produce all grades of peptic ulcer in susceptible animals. Sterile emulsions of the gastric mucosa, of the appendix, gall-bladder, or liver injected intravenously or intraperitoneally produce in animals a toxic serum. At the end of from ten to fourteen days this serum has such selective affinity that its introduction into the circulation of animals produces necrosis and ulceration in the organs from which the original cell emulsions were made. The toxicity of the serum persists and may produce its effects after more than a year. The serum gives the various test-tube reactions for immune bodies, namely, lysins and precipitins. The most pronounced reactions are with gastric cell emulsions. Their injection rapidly causes acute hemorrhagic ulcers, which ulcers may later become chronic. Saturation of the serum with gastric cells before injection, robs the serum of its toxic qualities. Bolton has called this immune serum "gastrotoxin."

Bolton's gastrotoxic serum appears to indicate that, as result of a wide variety of ailments or systemic constitutional affections, disintegration of body cells may occur. The initial agents causing the malfunction form a great and dissimilar group. The poisons elaborated are of specific nature with respect the tissue from which they are derived. It would seem that the demands constantly being made upon the stomach result in a great cellular waste. The cellular waste satisfies the essentials of a protein poison. When

opportunity occurs this poison is capable of producing local cell changes in the gastric mucosa, which changes furnish the *anlage* for a subsequently developing ulcer. Once this initial local injury has been done to the gastric lining, the autodigestion of the mucosa by gastric juice or its ability to harbor bacteria are possible, and *not until then.*

The above brief summary indicates that we cannot expect to ever establish a single definite cause of gastric ulcer. The immediate causes of ulcers vary widely and are highly individual. The essential point is that through some malfunction a point of least resistance occurs in the gastric lining and *normal* gastric physiology is permitted to produce an *abnormal* tissue change. *It would likewise appear that we have no basis for regarding gastric ulcer as a distinct disease entity.* It seems more proper to consider that ulceration of the gastric mucosa is a local accident in association with a systemic upset, the nature of which upset may be extremely varied. When once the damage has been done locally in the stomach wall, whatever may be the primary cause, the future course of the process is similar. Pepsin and hydrochloric acid attack the inert gastric cells, necrosis results and ulcer is established. The course of the process depends mainly upon the persistence of the underlying systemic causes, variation in the quality of the gastric juice, local intragastric trauma (as by food, bacteria etc.), and the influence of the intrinsic muscles forming the stomach wall. Such facts strongly suggest that *peptic ulcer presents aspects indicating its being a self-limited disease.*

3. *Histopathological.* From the inception of symptoms clinically, it is impossible to prognosticate the future course of any peptic ulcer. While many ulcers destroy relatively little gastric mucosa and produce harmless scarification, thus evidencing a tendency to spontaneous cure, other ulcers, seemingly equally inocuous clinically, progress rapidly through various pathological stages and are very shortly associated with stenoses, extensive callous formation, hemorrhage, perforation, or malignancy. However, chronicity in the histopathological sense by no means indicates that a peptic ulcer is old in terms of months or years. Malignant change in ulcer edges may occur quickly and in no way point to the long existence of a previously benign affection. It is of much significance to observe variation in the appearance of pathological transformations in ulcers situated similarly in various parts of the stomach. While fully 85 per cent. of all gastric ulcers occur in the pylorus, antrum, and along the distal four-fifths of the lesser curvature, and while in these positions the greatest damage can be done by ulcer, yet just as striking changes occur in ulcers situated in other portions of the viscus. It is of importance to note that fully two-thirds of the gastric ulcers occur in the portion of the stomach whose mucous membrane is not devoted to the elaboration and secretion of hydro-

chloric acid. It would also seem to be of significance to recall that the majority of peptic ulcers occur in that part of the stomach in which the greatest circulatory, muscular, and nervous activity is manifest; that the fewest ulcers occur in that portion of the viscus which is fixed and which has to perform mainly the duties of a food receptacle and an acid-secreting organ.

4. *Physiological.* (*a*) *Chemical.* It is a striking commentary upon the empirical nature of standard treatments of peptic ulcer that they have as their basis the principle that gastric chemistry has been greviously upset. It has been supposed that this disarrangement has been caused either by the development of ulcer or that the upset itself has produced the ulcer. This chemical disturbance is generally put down as being in the nature of an overproduction of acid gastric juice and pepsin. It is presumed that the so-called "corrosive effects" of this overactive digestive juice produces gastric ulcer or prevents healing of one already present. It is significant to observe, in the first place, that the normal gastric juice frequently varies in strength well beyond the range of the so-called increases which are often demonstrable when gastric ulcer exists. In a recent study of 500 cases of peptic ulcer, in but 40 per cent. did I find a free HCl concentration above 0.3 per cent. In 35 per cent. the acidity was well within the "normal" range, and that in the remaining 25 per cent. the acidity was reduced or was entirely absent. Similar observations have been recorded experimentally by Carlson, and in man by Rehfuss and his coworkers. Moreover, the portions of the stomach which are least the site of gastric ulcer are those in which, physiologically, the concentration of hydrochloric acid is greatest and where the acid is in nascent form. That there are causes of gastric ulcer other than the variation in the hydrochloric acid concentration is also supported by the observation that in bile-free stomachs large amounts of hydrochloric acid in the concentration of as high as 0.6 per cent. mixed with pepsin may be placed in the stomach and yet not produce ulcer. It is also evident that the primary damage which results in gastric ulcer is not dependent wholly upon acid gastric juice by the ancient observation that if this were the case the stomach would digest itself. Clinical and histopathological evidence indicate that when once the initial damage to the gastric lining has been brought about from whatever cause, digestion of partly devitalized or necrotic mucous membrane may occur with equal readiness in the presence of normal or even subnormal gastric acidity. With these facts in mind it seems strange that treatment of gastric ulcer has largely rested upon a chemical foundation, which chemical foundation was extremely unstable and shifting. It has been presumed that in ulcer stomachs, overacidity was present, and that this overacidity must be counteracted by alkalinization before healing could take place. It has been presumed that the pain of gastric

ulcer existed as a consequence of irritation and "corrosion" of raw mucous surfaces by gastric juice rich in hydrochloric acid and pepsin even though the researches of Pawlow, Rehfuss, Carlson, Hertz, Hamburger and others have demonstrated that pain is not uniformly present when gastric acidity is highest, and that in known ulcer cases the introduction of high percentages of acid fails to produce pain. The relief from pain in gastric ulcer cases is quite as prompt when alkalies are administered in low acid cases as when such are used in high acid cases. Prompt relief of pain in such instances is also secured by the exhibition of lavage, alcohol, opiates, diet, etc. It would seem, therefore, that medical treatment of peptic ulcer based upon chemical upsets supposed to be associated with the ailment presents much that is empirical, irrational, and unscientific.

(*b*) *Physiological Motor Consideration.* Modern physiological investigations have been especially rich in elucidating the motor activity of the stomach under normal and pathological conditions. For this knowledge we are indebted to the development of the roentgen-ray and the tireless researches of Pawlow, Cannon and his pupils, and to Carlson. These investigators have established the significance of certain gastric motor cycles. They have shown that these cycles occur with almost mathematical precision. Upon these constants it would appear to be possible to base clinical observations and therapy. It would also seem that the mechanical factors concerned with digestion are of greater importance than are variations in the secretory function. It is with the mechanical features in digestion that we purpose to deal in suggesting a rational régime in the treatment of peptic ulcer. In order to emphasize the points mentioned below in detailing the type of treatment which we advance, the chief facts established by physiological investigation with regard the mechanical activity of the stomach now will be summarized:

The fasting stomach is in a state of tonic contraction. It is rarely empty. Its contents contain both hydrochloric acid and pepsin. These secretions apparently aid in preserving gastric tone, in digesting mucus, dead bacteria, and desquamated cell detritus. Hunger is manifested by rhythmic gastric systoles. These precede appetite desire and cause an unpleasantness that leads to eating. Repeated swallowing motions cause inhibition of gastric tonus. Eating starts gastric-juice secretion. Food entering the stomach initiates the peristaltic movements peculiar to gastric digestion. These peristaltic movements continue so long as food remains in the stomach. They pass from the pars media toward the pylorus in rhythmic sequence in a given case with equal intensity, thus maintaining a constant pressure in the antrum. The proximal third of the stomach acts mainly as a sac or reservoir and is comparatively free from peristaltic activity. The acid reaction of con-

tents in the fundus of the stomach closes the cardia. The discharge of chyme from the stomach is intermittent. The pylorus opens only when acid gastric contents relax the sphincter. The presence of acid chyme in the duodenum closes the pylorus and keeps it closed until the duodenal juices have rendered its contents neutral or alkaline. Acid chyme stimulates the flow of pancreatic juice and bile. The peristaltic waves press acid chyme toward the pylorus and intimately mix gastric contents and digest them. Only after duodenal contents have become neutralized can the pylorus relax and acid chyme pass through. This alternate opening and shutting of the pylorus with discharge of chyme is continued until the stomach is empty.

Gastric Secretion and Gastric Emptying are Greatly Influenced by the Kind of Food Ingested. Water and normal salt solution cause limited gastric secretion and rapid stomach emptying. This rapid exit causes but feeble peristalsis. Carbohydrate foods leave the stomach quickly because on account of their failure to unite with acid gastric juice they permit a large amount of free acid to come into contact with the pyloric sphincter and thus conduce too rapid opening of the pylorus. Marked retardation in the discharge of carbohydrates occurs if such be mixed with alkaline solutions. The alkali delays the appearance of acid by checking temporarily the secretion of acid gastric juice and also by uniting with the free acid already poured out. The acid control of the pylorus is thus interfered with and emptying is delayed. Protein food leaves the stomach slowly because proteins join with free HCl and thus for a time retard the development of an acid reaction which initiates pyloric opening. Protein has also been shown by Khingine to cause the secretion of 50 per cent. more gastric juice during the first four hours of digestion than when carbohydrate is fed. When such protein is passed into the duodenum there is more acid to neutralize than when carbohydrate was fed, consequently the pylorus remains closed for a longer time and the antrum of the stomach is subjected to intense peristaltic activity without pyloric relaxation. It is estimated that in such event the peristaltic waves number from 300 to 500 per hour. Cannon states that at the end of a half-hour eight times as much carbohydrate as protein has been absorbed, and there exists twice as much carbohydrate as protein in the jejunum. While carbohydrates begin to leave the stomach at once, proteins are delayed from one to three hours. Fats remain longest in the stomach because they excite little free HCl production and consequently the acid control of the pylorus is reduced to a minimum.

Vigorous mixing of food with acid chyme occurs in the antrum and pylorus, the zone in which 60 per cent. of all gastric ulcers are found. Food delay in this locality permits of increased local movement of the viscus, greater opportunity for food and acid to remain in intimate contact with injured gastric lining, hence, opportunity

for the maximum of trauma, infection, digestion of damaged tissue, stress on the pyloric sphincter, and local alterations in circulatory and neuromuscular mechanism.

The facts which I have enumerated have been established as constants by repeated laboratory and clinical investigation. In my opinion they furnish a logical ground-work for the treatment of peptic ulcer. They place such treatment upon a rational basis and remove from it many purely empirical and "rule-of-thumb" features which characterize commonly accepted modes of therapy. I am convinced of its clinical usefulness after five years of careful clinical observation.

5. *Selection of Cases for Types of Treatment.* The principles involved in treatment of gastric ulcer, of whatever nature, first demand *search for and eradication of the primary systemic fault.* Often the localization of such is difficult. Inasmuch as foci of infection may exist in oral adenoid tissue, head sinuses, about teeth or in systemic lymph gland chains, these must be removed promptly. Intra-abdominal infections must likewise be eradicated, *e. g.,* diseased appendix, gall-bladder, Fallopian tubes, ovaries, ulcers, or subinfections of the bowel. It would appear quite inadequate to remove external local foci of infection and to leave behind intra-abdominal foci containing bacteria already accustomed to their environment and ready to spread their operations to the gastric lining when opportunity offers. It would appear that the removal of these variously situated germ centers constitutes a fundamental step toward the cure of gastric ulcer.

After local foci of infection have been removed the mode of treatment is further influenced by the *type* of ulcer that has been proved to exist. Unless ulcers with much scar or causing great gastric deformity are demonstrated to be luetic, little hope of permanent relief by medical measures can be offered. Surgery promises the greatest prospect of relief to such cases. Intense pain, frequent hemorrhage, perforation, or the danger of malignant change taking place in calloused ulcers likewise contra-indicate non-operative care. Unfortunately we have no clinical or laboratory tests which indicate to us *what type* of ulcers will become malignant or *when* early malignant change is taking place. The roentgen demonstration of calloused ulcer exceeding 2 cm. diameter when such is associated with history of frequently recurring ulcer symptoms and positive chemical test for blood constantly determined in the stools, forms a clinical hint that malignancy can be expected. The most competent clinicians are agreed that calloused, recurring ulcers, located in the pyloric end of the stomach should be treated operatively. Excision should be performed when mechanically possible. If excision is impracticable, then infolding, or cautery puncture, with or without gastrojejunostomy, yields the most satisfactory results. In non-obstructing ulcers, gastrojejunos-

tomy should always be accompanied by permanent pyloric closure. Gastrojejunostomy properly performed acts by aiding gastric emptying, by diminution of free HCl (an average of 18.2 points in 196 consecutive cases in our series), and by permitting limited jejunal regurgitation into the stomach.

Successful medical treatment of ulcer thus first demands careful selection of cases to be so treated. It is indicated only in ulcers associated with little callus, or if calloused, located in portions of the stomach in which stenoses are not liable to result or where surgical procedures cannot be carried out. Certain essential principles are to be borne in mind in carrying out medical treatment.

II. Outline of Author's Method of Non-surgical Treatment.

1. *Rest in Bed.* Both physical and mental for from one to three weeks. Bodily and psychic activity stimulate peristalsis.

2. *Rest to the Stomach Itself.* When it is recalled that during an ordinary meal the digestive processes demand more than 2000 peristaltic waves, the effect of such as a mechanical irritant to an ulcer or the ulcer-bearing area cannot be disregarded. Complete rest for the stomach also demands avoidance of irritating medicine, gastric lavage, and frequent abdominal examinations of the suspected focus.

3. *Local Applications to the Abdomen.* Painful spasms are further prevented by having constantly applied to the abdomen compresses saturated with Ochsner's fluid (alcohol and boracic acid.)

4. *Keeping the Stomach Empty of Food.* This promotes healing by limiting local irritation from the food itself, from reducing the amount of gastric juice required to digest food, by limiting gastric peristalsis and avoiding painful gastrospasms which limit free circulatory interchange. The abstinence from food by mouth should be insisted upon for from three to seven days, according to the case. The period of fast is determined best by clinical disappearance of gastric spasm (pain, regurgitation, waterbrash, heartburn) and by fluoroscopic proof of absent or diminished gastric peristalsis. During the fast *paraffin wax is chewed* for fifteen minutes every hour. It keeps the mouth clean, promotes free flow of protective saliva and mucus, counteracts painful hunger contractions and gastrospasms, and allays thirst.

5. *Rectal Feeding.* During the fasting period, rectal feedings are instituted. From 500 to 1000 calories of nutrient mixture are given in twenty-four hours. We use a clystra containing 1 ounce of 50 per cent. alcohol, 1 ounce of glucose with normal salt solution to make 240 c.c. The nutrient enema is given at body temperature by the drop method. The drops flow at the rate of 30 to 60 drops per

minute. During the first day of rectal feeding, gtt. x of tr. opii are given with each enema.

6. *When Mouth Feeding is Begun.* Usually from the fourth to seventh day. Two factors control the choice of diet: (*a*) nourishment should be liquid and administered warm in small quantities frequently, and (*b*) carbohydrates should be selected.

(*a*) Small quantities of liquid food should be frequently administered in order that the stomach empty rapidly with the least effort and thus remain food-free for the longest time, thereby giving maximum time of rest for ulcer healing. The duodenal digestion must be called upon until gastric conditions warrant demands being made upon stomach digestion. Keeping the stomach food-free keeps hydrochloric acid or pepsin production to a minimum. From 4 to 6 ounces of warm liquid are given every hour.

(*b*) As experimental facts have established, carbohydrate foods leave the stomach most quickly. Therefore, liquid carbohydrate mixtures (barley water, rice gruel, thin cream of wheat, thin creamed vegetable soup, etc.) are fed. Milk is not given as routine. Milk results in almost pure protein clots in the stomach. These act as do other proteins and remain for a long time in the stomach as a source of irritation, as stimuli to acid secretion and as choice culture media for bacteria. If milk be given at all, it should be first parboiled or predigested. Carbohydrate liquids produce the least secretion of HCl and pepsin and are weak stimuli of gastric peristalsis and impose the minimum of work upon the duodenum. It should be recalled that the pylorus opens only when the duodenal contents are neutral or alkaline. If the gastric contents are of such nature as to impose slight demands upon the stomach secretions and motility, the duodenum has little work as a neutralizer to perform and the pylorus remains free from spasm and opens readily. There are thus avoided gastric stagnation and accumulation of distressing free and combined acids, which prevent healing and which usually demand frequent lavage or the exhibition of large quantities of alkali.

7. *Limitation of Overproduction of Gastric Acid.* This is obtained by keeping the stomach food-free as above described. This secondarily limits both the frequency and the strength of gastric peristaltic waves. Unless food leaves the stomach rapidly, gastric glands continue secretion and coincidently stress of gastric peristalsis upon the pylorus keeps up constant irritation of ulcer-bearing areas.

If the above points established by modern physiological research are borne in mind, the exhibition of large quantities of alkali are unnecessary. Their use is certainly unscientific. Providing the gastric lumen is patent, the stomach empties freely. There is no stagnant, irritating, fermenting residue. Large quantities of alkali, according to Pawlow and to our clinical and laboratory experience, create pernicious increases of gastric acid and of mucus and generally

demand relief by lavage. Moreover, we have shown that many gastric ulcer cases do not exhibit hyperacidity or hypersecretion. It is true that the stomach *can* neutralize large quantities of alkali if compelled to do so, but there is no physiological reason why it should be called upon to thus overwork. It will be remembered that the normal habitat of gastric epithelium is an acid or at the best a neutral medium. If these epithelial cells are called upon to live in an excess of alkali, they live, as it were, in the presence of a foreign body. Experiments in artificial tissue growth have shown that cell proliferation is retarded by hyperisotonic alkaline solutions. Hence, overalkalinization may prevent healing. Attempts at protection from this foreign body (excess alkali) are shown (1) by the acid-producing glands oversecreting, and (2) by the mucoid degeneration of physiological fatigue which results in the throwing out over the secretory glands of a protective layer of mucus. The vicious circle thus formed results in enormous secretion of acid and mucus and is doubtless at least a partial explanation of the so-called hypersecretion associated with gastric ulcers, particularly when such are treated by the overalkalinization method. To combat this condition of affairs the patient's stomach must be washed frequently or greater quantities of alkali must be given in order to overpower the stomach's defensive mechanism and produce fatigue or exhaustion of the acid-secreting mechanism. It is a common observation that those patients who are treated for ulcer by the overalkalinization procedure always require frequent gastric lavage in order to ensure their comfort. This frequent lavage is to be condemned not only on account of its disagreeable features but because it acts contrary to the primary requirement of healing, namely, *rest of the affected part*. It is quite evident to those who have watched the behavior of a stomach by means of fluoroscopic screen when a tube is inserted into it that gastric lavage defeats this primary principle of healing. Lavage is generally accompanied by vigorous gastric contractions that persist not only during the maneuver but often for a long time afterward. If dieting is arranged on the carbohydrate basis, alkali is given in only sufficient quantities to keep the stomach slightly acid or neutral and to neutralize the duodenum, thus aiding in pyloric relaxation, gastric lavage need rarely be instituted during the entire course of a patient's treatment. In the past five years we have not employed lavage therapeutically in ulcer cases more than a dozen times. Lavage is so rare a procedure in my clinic that my associates and patients consider such an order as almost contra-indicated. It is readily judged how a treatment of which lavage does not form a prominent feature contributes much to a patient's peace of mind and shortens the period of hospital incarceration.

8. *Medical Treatment.* It is doubtful if any form of medicine has a direct healing effect upon peptic ulcer. Medicines are adminis-

tered largely to counteract discomfort due to three main causes, namely, (*a*) painful gastrospasms, (*b*) accumulations of overacid gastric contents associated with peristaltic unrest, (*c*) pain associated with perforation.

(*a*) *Painful gastrospasms* are usually controlled by carrying out the dietetic principles which I have above mentioned. The chewing of paraffin wax relaxes the pyloric spasm largely through stimulating a proper swallowing reflex and by fatigue of hunger-like contractions. Certain types of case in which there is an individual vagus hypertonia, or when ulcers are located at or near the orifices, demand the exhibition of antispasmodic medicines, such as atropin, tincture of belladonna, or bromides. In the early stages of the treatment, when the stomach is being kept as free as possible of contents, atropin may be given hypodermically or bromides may be placed in the nutrient enemata. Later, when food is being given by mouth, tincture of belladonna in doses of from 5 to 15 drops may be administered fifteen minutes before feeding from three to six times daily. We have not found useful, as analgesics, the exhibition of large doses of such "protective" medicines as bismuth and olive oil. These medicines doubtless act by affecting the rate and intensity of peristalsis, although they may have some effect in proved cases by direct action upon the ulcer. At times orthoform, given in 10-grain doses, in warm water, is an efficient local anesthetic when it is able to come in direct contact with an open ulcer.

(*b*) *For the relief of overacid gastric accumulations*, sodium bicarbonate is contra-indicated, because its administration results in the production of annoying accumulations of carbon dioxide with resultant gastric retention or painful belching, and because its neutralizing value is comparatively low. Large quantities of bicarbonate of soda are necessary to give relief, and the administration of such secondarily produces excessive gastric secretion. If alkalies are indicated, better results are obtained by the exhibition of frequent small doses of milk of magnesia or calcined magnesia. The ordinary case is very comfortable when from five to ten grains of calcined magnesia are given every two or three hours. Many cases require no exhibition of alkali if the physiological principles above outlined form the basis of the treatment. Only in very extreme cases is it necessary to employ gastric lavage. When it is employed, warm Carlsbad water (1 dram of artificial Carlsbad salts to 1 quart of water) may be satisfactorily administered. Usually the exhibition of atropin or belladonna for the relief of gastrospasms exerts a definite effect toward controlling oversecretion of acid gastric juice.

(*b*) The acute prostrating *pains of perforation* are best controlled by the prompt administration of morphin hypodermically, rest in bed, and hot compresses to the abdomen. Only prompt surgery saves the patient's life.

9. *Hemorrhage.* Constant seepage, demonstrated either microscopically or clinically, is generally an indication for abdominal section. Intermittent seepage may be controlled best by rest in bed, morphin hypodermically, intravenous injections of fresh horse serum, coagulose, or by copious transfusion of whole blood. In acute hemorrhage accompanied by vomiting, prompt lavage of the stomach with water at 110° F. frequently stops both the vomiting and the hemorrhage. The exhibition of morphin, rest in bed, and whole blood transfusions generally prevent recurrence of hemorrhage. In this class of case, however, surgical intervention should be resorted to early, and this especially if in a given patient, frequent, copious, prostrating hemorrhages occur.

10. *Bowels.* During the early periods of treatment, simple soapsuds enemata may be administered every second day. After the second week, morning doses of phosphate of soda or Carlsbad salts in hot water may be applied. In chronic cases, liquid paraffin given in equal quantities of warm cream result in easy motions, and the paraffin appears to have certain protective value upon the ulcer bearing area.

Summary of the Author's Dietetic Régime in Treatment of Peptic Ulcer.

Days 1 *to* 7 (Time varies as outlined in above description of treatment).

By Mouth. One-half ounce warm water hourly when awake. Patient chews paraffin wax for fifteen minutes at least once in two hours. Juice of sweet orange or grape fruit occasionally.

By Rectum. Nutrient enema consisting of 50 per cent. alcohol 1 ounce, glucose syrup 1 ounce, and normal salt solution 6 ounces every four hours. The enemata are preceded by a cleansing irrigation of the colon with normal salt solution. They are given at body temperature by the drop method at the rate of from 30 to 60 drops per minute. Calories daily approximately 1000. During the first two days, tr. opii ℥x is added to each second enema.

Days 3 *to* 14 (case of average severity).

By Mouth. From 4 to 6 ounces of water gruel at temperature of 100° F. The gruel is taken slowly through a glass tube. Gruels are made from rice, cream of wheat, oatmeal, sago, corn-meal, malted milk, macaroni and vermicelli, rusks, potato, asparagus, cauliflower, beans, peas, and boiled onion. They are strained before feeding. Flavoring with coffee, chocolate, vanilla, caramel, etc., renders the cereal gruels palatable and their administration easier. To the vegetable gruels small quantities of arrowroot or corn-starch are added to secure a thin emulsion.

Before each feeding, paraffin wax is chewed for five minutes. Warm water or sweet orange or grapefruit juice are allowed as desired, but never in greater quantity than 1 ounce at a time.

By Rectum. During the first two days of mouth feeding, two alcohol-glucose-saline nutrient enemata are given. During the second two days, *one* such nutrient enema is administered. After the fourth day of mouth feeding no rectal feedings are given in the average case. Calories approximately 800.

Days 14 to 21.

6.30 A.M. A glass of hot water and 1 teaspoonful of non-effervescent sodium phosphate.

7.30 A.M. One ounce of sweet orange or grapefruit juice, 2 ounces of thin cream of wheat, or farina, or well-cooked rice, or corn-meal, 2 ounces of skimmed, parboiled milk, may be taken with cereal, and if desired a small quantity of powdered sugar used; 1 zweibach with a thin layer of fresh butter, 4 ounces of parboiled skimmed milk, containing half volume of lime-water, served warm and flavored with coffee, cocoa, caramel, or vanilla.

9.30 A.M. Six ounces of thin water gruel from cereals or fresh vegetables, strained and served hot, 1 rusk or zweibach, or dry toast.

11.30 A.M. Four ounces of malted milk, whipped egg, with parboiled milk, corn-starch pudding, simple custard lightly cooked.

12.30 P.M. Six ounces potato, pea, bean, or asparagus puree, (strained), or vegetable broth; 4 ounces of salisbury steak (moderately well cooked) to chew; 2 ounces (cooked weight) of thin rice, sago, tapioca, or corn-starch pudding made with parboiled milk and egg yolk; 2 ounces of parboiled milk and small quantity of pulverized sugar may be eaten with the pudding; 1 rusk or zweibach, 6 ounces of parboiled milk and quarter volume of lime-water flavored to taste.

4 P.M. Four ounces of water gruel from cereals, 1 very soft poached egg, 1 rusk or zweibach, 4 ounces of hot Vichy water.

6 P.M. Four ounces of whipped egg, 2 rusks or zweibach, 6 ounces of malted milk (thin), flavored to taste, or cereal water gruel or parboiled milk and quarter volume of lime-water gruel.

9 P.M. Six ounces of water cereal gruel or 4 ounces of malt marrow, 2 graham crackers. Calories approximately 1500.

Days 21 to 42.

6.30 A.M. Two teaspoonfuls of phosphate of soda in a glass of hot water.

8 A.M. Juice of 1 sweet orange or half sweet grapefruit, or boiled prunes passed through fine collander; 2 ounces (cooked weight) of thin cereals (cream of wheat, farina, oatmeal, corn-meal) 2 ounces of skimmed milk and small amount powdered sugar, 1 soft poached egg, 2 zweibach, 2 rusks or 2 thin slices of well-toasted graham bread, 1 pint of hot skimmed milk + a quarter volume of lime-water flavored to taste (cocoa, vanilla, etc.).

10 A.M. One pint of hot parboiled whole milk and fifth volume of lime-water, 2 rusks or graham crackers.

12.30 noon. Four ounces of creamed soup from vegetables, strained, 6 ounces rare meat to chew, 4 ounces well-mashed potato or baked potato (mealy inside), or carrot, peas, beans, cauliflower, Brussels sprouts, or asparagus (all vegetables passed through a strainer and served with 15 grams of butter), 4 ounces (cooked weight) of pudding from rice, corn-starch, sago, tapioca, cream of wheat, or farina or 4 ounces of custard, pulp of sweet orange, grapefruit, or prune whip, or chew 6 ounces of watermelon or cantaloup, half pint of hot skimmed milk.

3.30 P.M. One hundred and fifty c.c. of hot whole milk and quarter volume of lime-water or 150 c.c. of malted milk or weak cocoa.

6.30 P.M. Two rusks or zweibach or 2 slices of well-toasted graham bread, 2 very soft poached eggs, 100 grams of sweet apple sauce or 1 baked apple (omit skins), or juice of sweet orange or half of grapefruit, or chew 6 ounces of melon, 1 pint of skimmed milk, hot.

9 P.M. Two hundred and fifty c.c. of whole parboiled milk and quarter volume of lime-water of 250 c.c. of malted milk, hot. Calories for twenty-four hours approximately 2000.

General Diet after Three Months. If distress, patient should go back to 7 to 21 day diet.

7 A.M. One pint of skimmed milk and half-gill of cream.

9 A.M. Two pieces of toast without butter, juice of one sweet orange or grapefruit or ripe melon or apple sauce or baked apple (do not eat skin) or marmalade, 1 dish or well-cooked cereal (oatmeal, farina, or cream of wheat), 2 very soft poached eggs, 2 cups of hot, sweetened water. The water may be made more palatable by flavoring with cocoa, tea, coffee, or cream.

11 A.M. One cup of bouillon (two cubes), two graham crackers.

1 P.M. This should be the heavy meal of the day. It may consist of meat (rare beef, rare hamburger steak, lamb, or white meat of fowl), fish (never fried), oysters, well-cooked spinach, cauliflower, carrots, squash, peas, (hulled), string beans, Brussels sprouts, baked or mashed potatoes (in moderation), rice with gravy, simple puddings made from cereals, corn-starch, gelatine, well-cooked fruit sauces, simple cakes, no white bread (all bread should be made from dark flour and should be at least one day old), 1 pint of skimmed milk taken hot.

4 P.M. One glass of hot peppermint water (20 drops of "essence" of peppermint to the glass), sweeten to taste and drink slowly; two graham crackers.

7 P.M. A light lunch consisting of vegetable soup, simple salad, toast, soft eggs, and plain puddings or cake, with or without ripe cooked fruit sauces; 1 pint of hot skimmed milk.

Bedtime. One glass of malt marrow, malted milk, or hot skimmed milk. Calories approximately 3560 for twenty-four hours.

THE OPERATIVE TREATMENT OF HYDROCEPHALUS: A PRELIMINARY REPORT OF FORTY-ONE PATIENTS.[1]

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The treatment of hydrocephalus has been most discouraging. One operative method after another has been advocated as a possible means of successful drainage in these patients; one or more cases are reported and then nothing more is heard of the method, the patients having died and the method no longer used. Frequently a "new" method of drainage is published more upon a theoretical basis rather than upon practical applicability; one case alone is published as having been operated upon and the result was death; surely, we must grant that the method may have been new, but the result has been the same as in the earlier methods of treatment, and unless the percentage of cures, or even improvement, can be raised, such methods are naturally soon discarded.

The chief cause of failure in these methods of drainage is, in my opinion, not due so much to the ignorance regarding the nature of hydrocephalus itself, what the cerebrospinal fluid really is, its method of secretion and excretion and similar points of almost total obscurity, but rather to a lack of appreciation of the fact that the condition of hydrocephalus is rarely limited to a dilatation of the ventricles alone—that is, the so-called hydrocephalus interna, which is the result of a blockage of the escape of cerebrospinal fluid from the ventricles into the subarachnoid spaces by an obstruction of the adequate of Sylvius or of the foramina of Majendie and Luschka; but, on the contrary, the condition is most frequently due to a lessened excretion of the cerebrospinal fluid through the subarachnoid cranial and spinal veins, the sinuses, possibly lymphatics, etc., so that the type of so-called hydrocephalus externa is developed. It is this latter condition of so-called hydrocephalus externa that is most frequent and yet the methods of treatment have been almost all of them directed to a drainage of the ventricles in the condition of hydrocephalus when it is a fact that the ventricles do not require drainage in only a small percentage of these cases; they are not dilated in the majority of cases because the aqueduct of Sylvius and the foramina of Majendie and Luschka are not obstructed, and there is a free escape of cerebrospinal fluid from the ventricles into the subarachnoid spaces, so that any operation merely directed to connect the ventricles with the subarachnoid or subdural spaces in those cases is of no possible benefit. In the comparatively rare cases, however, of true hydrocephalus interna due to a definite

[1] A complete report of the cases in detail will be published later.

blockage of the aqueduct of Sylvius or of the foramina of Majendie and Luschka by a subtentorial lesion, those methods of drainage are logical, and yet I believe they are of very limited usefulness in that the condition of hydrocephalus interna is almost always, in my opinion, the result of an early diffuse meningitis, the results of which (adhesions, exudate, thickenings, etc.) may not only block the escape of cerebrospinal fluid from the ventricles into the subarachnoid spaces, but also so impair and even completely block the channels of escape of the cerebrospinal fluid through the cortical veins, sinuses, possibly lymphatics, etc., so that even if the ventricles were connected with the subarachnoid spaces, yet the cerebrospinal fluid would not be drained from the cerebrospinal canal; that is, the condition of blockage of the escape of cerebrospinal fluid is a diffuse one rather than a mere obstruction of the ventricles; there are cases, to be sure, of hydrocephalus interna due to a tumor or cyst formation blocking the aqueduct of Sylvius or the foramina of Majendie and Luschka, and where the ventricular subarachnoid method of drainage would be logically applicable, but these cases form but a very small percentage of the large group of hydrocephalus patients; in this series of forty-one patients, twenty-six were of the external type, whereas only fifteen were of the internal type of hydrocephalus; besides, the method of draining the cerebrospinal fluid described in this paper can be used in either condition—that is, whether the condition is one of the internal or of the external type of hydrocephalus. The condition of unilateral hydrocephalus may be mentioned as a very rare occurrence; it is due to a blockage of the aqueduct of Sylvius and the opposite foramen of Monro; one of our patients was of this type.

In order to differentiate whether the condition is one of hydrocephalus interna or of externa, or of both (and this last condition occurs fairly frequently), the method of Dandy and Blackfan[2] in their excellent monograph can be used whereby the time of excretion of phenolsulphonaphthalein first from the ventricles and then from the spinal subarachnoid spaces can be observed and the amount estimated in the urine; if practically of equal duration and amount then the ventricles are not blocked and the condition is one of hydrocephalus externa, or of both, whereas, if the excretion of phenolsulphonephthalein injected into the ventricles is greatly delayed and lessened in amount in the urine, then the ventricles are blocked and the condition is one of hydrocephalus interna. A much more simple method, however, can be used, and I believe it is of sufficient accuracy to warrant its use whenever a differentiation of the two conditions is desired in the treatment of hydrocephalus. I make this statement because the operative method to be described in this paper makes such a preliminary test unneces-

[2] Am. Jour. Dis. Child., December, 1914, pp. 406–482.

sary, as the differentiation of the internal from the external type of hydrocephalus can be ascertained at the time of the operative procedure and treated accordingly through the same operative incision and at the same time. If, however, it is desired to ascertain the type of hydrocephalus before the operation, then a ventricular puncture needle can be inserted into the ventricle through a very small skin incision at the anterior fontanelle as far from the median line as possible, and at the same time a spinal puncture needle is inserted into the lumbar subarachnoid space; with the patient lying upon his side, the median line of the head being upon an exact level with the spinal canal and the patient being perfectly quiet, the pressure and rate of flow of the cerebrospinal fluid from both the needles should be the same if the ventricles and subarachnoid spaces are in free communication; the condition would therefore be one of hydrocephalus externa. If, however, the ventricles are blocked, then the pressure and rate of flow of cerebrospinal fluid from the ventricle needle is greatly in excess of that from the spinal puncture needle, which may be but a few drops; the condition therefore would be one of hydrocephalus interna. Another aid in the differentiation in the older children may be found in the roentgen-ray—the internal type producing convolutional markings throughout the vault of the skull, whereas this would naturally not occur in hydrocephalus externa.

Many operative procedures have been used in the past to combat the condition of hydrocephalus. In the early days of Hippocrates merely repeated lumbar punctures and ventricular punctures were performed, but the result was invariably the same—a steady advance of the condition and frequently a much more rapid progress following the tapping, as though the sudden removal of the increased amount of the cerebrospinal fluid stimulated in some way a greater secretion of the cerebrospinal fluid so that the condition rapidly became worse. Occasionally, however, a case has been reported improved by such treatment; such cases, however, were rare and the reports of them were seldom made after one year had elapsed; they may have been, therefore, merely temporarily benefited. Drainage of the cerebrospinal fluid externally to the skin has almost always resulted fatally on account of the consequent infection and the resulting meningitis.

For these reasons many complicated and most tremendous operations have been devised to drain successfully the cerebrospinal fluid from the ventricles and the subarachnoid spaces, and all of them have been most disappointing.

Draining the cisterna magna (fourth ventricle) into the adjacent sinuses or into the pleural cavity by means of strands of various material through a suboccipital opening; connecting the spinal subarachnoid canal with the retroperitoneal space by means of a laminectomy and a laparotomy (and naturally limited to cases of

external hydrocephalus); joining the third ventricle to the subarachnoid spaces by means of a tube through the corpus callosum and the various other methods described in the literature—usually these methods have been abandoned after a few patients have been operated upon with the usual result—little or no improvement and only too frequently the death of the patient. Naturally, the condition is a most serious one and even the most dangerous operative procedures can be considered; no operation, however, should be advised to drain the ventricles unless it is definitely known that the ventricles are blocked and that the condition is not one of hydrocephalus

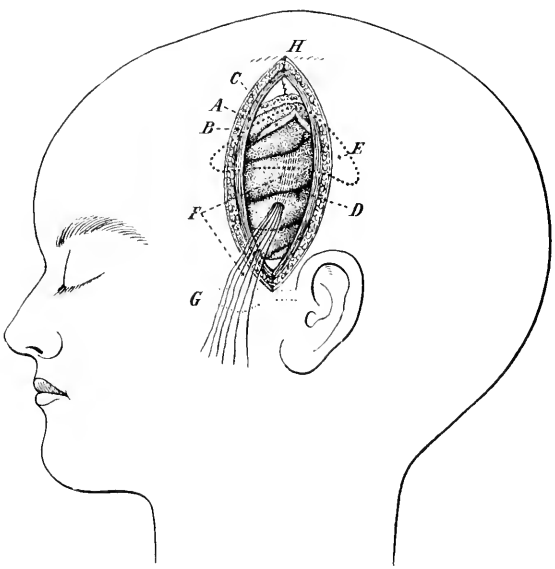

FIG. 1.—Diagrammatic sketch showing, through retracted temporal muscle (*A*), temporal fascia (*B*), and opened dura (*C*), the underlying cerebral convolutions and the Sylvian fissure (*D*). The dotted triangle (*E*) represents the lateral ventricle with the six linen strands (*F*) extending out from the ventricle through the upper temporal convolution beneath the Sylvain fissure. The scalp incision extends from the zygomatic arch (*G*) to the parietal crest (*H*).

externa. This fact has been so frequently overlooked that I feel that many needless and most tremendous operations have been preformed for the condition of hydrocephalus interna, which was not present—merely a hydrocephalus externa.

If we exclude those cases of internal hydrocephalus due to a tumor or cyst formation in the posterior midbrain and subtentorially producing a direct pressure blockage of the ventricles it is my belief that practically all of the cases of hydrocephalus are the result of a diffuse condition—an original meningitis in its various forms; if its consequent adhesions and exudative thickenings are so situated

as to block the exit of the cerebrospinal fluid into the subarachnoid spaces either in the aqueduct of Sylvius or at the foramina of Majendie and Luschka then we shall have produced the internal type of hydrocephalus; however, if the resulting adhesions, thickenings, etc., are not so situated as to block the ventricles, an internal hydrocephalus naturally does not occur, but still we shall have formed the external type of hydrocephalus because the cerebrospinal fluid cannot escape from the subarachnoid spaces of the cerebrospinal canal through its veins, sinuses, possibly lymphatics, etc., on account of their thickened walls and blocked stomata of exit due to the former meningitis of varying degree. Naturally, no

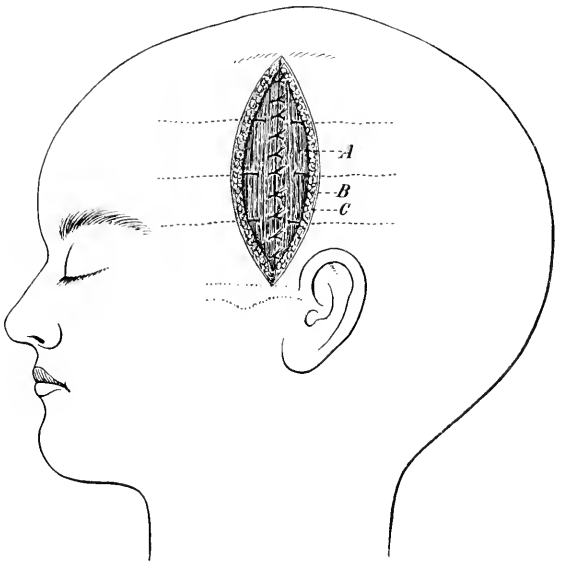

FIG. 2.—The six linen strands are brought out through the sutured temporal muscle (*A*) and temporal fascia (*B*) (to be sutured), and their ends are placed beneath the scalp (*C*) in the subcutaneous tissues—rich in lymphatics.

operative procedure merely designed to drain the ventricles into the subarachnoid spaces would be of any definite benefit in these cases; even if the openings of such drainage tubes did not themselves become blocked (and it is rare for them not to become blocked by adhesions, surrounding tissues, etc.), we should merely have the condition of internal hydrocephalus changed to one of external hydrocephalus, which is, to be sure, possibly a less serious condition in that the cerebral cortex is not so compressed and thinned as results from ventricular dilatation; besides, some cerebrospinal fluid may now escape through channels of exit only partially obstructed, and so a slight improvement is possible; however, unless the condition of external hydrocephalus is relieved so that the cerebrospinal fluid

can escape from the subarachnoid spaces and the cerebrospinal canal then the end result is merely delayed; a normal child is impossible.

It is interesting to note that epilepsy occurs more frequently in the external type of hydrocephalus than in the internal type; this may be due to the greater cortical irritation of this supracortical blanket of cerebrospinal fluid in these cases and also to the possibly greater corticomeningeal damage at the time of the original meningitis. Again, the great frequency of spina bifida associated with hydrocephalus merely illustrates the etiological factor in their production, a meningitic blockage of the stomata of exit in the walls of the veins, sinuses, possibly lymphatics, etc., so that the cerebrospinal fluid cannot escape from the spinal canal;[3] therefore an increased intradural pressure results in a protrusion and hernial sac formation in the lumbar region, the weakest and the latest region of the spinal closure; the fact that spina bifida occurs in about 35 per cent. of the cases of hydrocephalus, and that it is almost never associated with the internal type of hydrocephalus merely emphasizes the method of its production—that is, an early meningeal inflammation with a general blockage of the cerebrospinal fluid causing an increase of the intradural pressure so that the hernial protrusion of a spina bifida results with or without an external hydrocephalus; it is most rare, however, for a spina bifida to occur without there being definite signs of a mild external hydrocephalus.

Again, it has frequently been observed following the repair of a spina bifida, especially within a few days after birth, that a marked enlargement of the head occurred in a large number of the patients; this condition of external hydrocephalus might have resulted whether the spina bifida had been operated upon or not; but it does seem that the operative repair of the spina bifida by the removal of the large hernial sac, might have lessened the excretory surface of the cerebrospinal canal to such an extent that an increased amount of cerebrospinal fluid collected sufficient to cause the head to enlarge; it should be stated, also, that in these children the early operative removal of the spina bifida protrusion is usually performed when the hernial sac is enlarging, and thus the safety valve, as it were, of the increased intradural pressure, due to a blockage of the cerebrospinal fluid, is removed, and therefore the head, the next weakest portion of the cerebrospinal canal, will enlarge unless the fluid can be successfully drained.

In three patients I have been obliged to use the cranial method of drainage described in this paper after the spina bifida had been repaired. However, in this series of 41 patients an external hydrocephalus appeared several weeks after birth in 9 patients having the condition of spina bifida which had not been operated upon;

[3] Sharpe. Norman: Spina Bifida; an Experimental and Clinical Study, Ann. Surg., February, 1915, pp. 151–165.

in these cases it would seem that the spina bifida relief of the increased intradural pressure was not sufficient to prevent an enlargement of the head.

In this series of 41 operated patients we have used the same method of drainage, except in the first 2 cases, upon whom merely a bilateral subtemporal decompression was performed. Thirteen of the patients died, all of them with the exception of one child within thirty-six hours after the operation; that is, they could not survive the operative shock due to the sudden loss of a large amount of cerebrospinal fluid (this loss is now controlled and greatly lessened by elevating the head of the patient at the time of the ventricular opening). These patients were of the extreme type, very much emaciated, owing to their difficulty in swallowing, and were therefore bad operative risks. Of the remaining 28 patients upon whom the operation has been performed the results have been most encouraging. Their ages ranged from ten days to four years; naturally, the younger the child the less damaged is the cerebral cortex by the increased intracranial pressure; besides, the younger children stand the operative procedure as well and possibly better than the older ones, due most probably to the fact that many of the younger children are in a better physical condition than the ones subjected to a high intracranial pressure for a longer period of time; also to the fact that the cortical cells are not so highly developed in the younger children, and therefore they are apparently less upset by the operative procedure.

The object of the operation has been to drain permanently the ventricles (in the internal type of hydrocephalus) and the subarachnoid and subdural spaces (in the external type of hydrocephalus) outward beyond the cerebrospinal canal, that is, beyond the dura into the subcutaneous tissues of the scalp, a most absorptive area being well supplied with lymphatics. As drainage tubes buried in the body tissues always become blocked by adhesions, connective tissue, and surrounding tissues, etc., six linen strands are therefore inserted into the ventricles in the internal type and merely into the subarachnoid and subdural spaces in the external type of hydrocephalus and their ends brought out through the temporal muscle and temporal fascia beneath the scalp in a stellate manner; as these linen strands cannot be absorbed in the body tissues until four to six months have elapsed it is hoped that by the time of their absorption these artificial channels would be lined with endothelium or epithelium and thus their permanency and patency be assured.

In the laboratory the experimental production of internal hydrocephalus in puppies of ten days and two weeks of age has been performed by the method described by Dandy and Blackfan; that is, the aqueduct of Sylvius was blocked by a cotton plug through a suboccipital exposure; within twelve hours the ophthalmoscope

revealed choked disks of varying degree showing high intracranial pressure due to a blockage of the ventricles; unless this condition was relieved a secondary optic atrophy would result (as was permitted to occur in one dog so that it apparently became blind.)[4] In the other dogs which survived the first operation of ventricular blockage a subtemporal decompression was now performed (in three dogs a bilateral opening was made), and the linen strands inserted into the lateral ventricle and allowed to extend outward through the cortex, the opened dura, through the temporal muscle and temporal fascia into the subcutaneous tissues of the scalp. It was most interesting to observe a gradual subsidence of the choked disks in all but three of these nine dogs; in none of them, however, did the eye-grounds become as normal as before the operation, there being always an edematous blurring of the optic disks showing that the relief of the ventricular blockage had not been entirely complete. These dogs all died (three of them as a result of the internal hydrocephalus), within ten weeks after the drainage of the ventricles with the linen strands, which had therefore not yet been absorbed; so that it was still not ascertained whether the artificial canals formed by the linen strands would have remained as permanent patent channels of drainage for the cerebrospinal fluid or not.

However, one of the children having the condition of external hydrocephalus upon whom I had performed a right ventricular drainage on June 19, 1916, and then a left ventricular drainage on July 7, 1916, this child after making a definite improvement and three months after the first drainage operation, fell out of a high chair at home on September 9, 1916, fracturing the base of the skull. It was brought to the Polyclinic Hospital upon my service and died on October 13, 1916. An examination of the brain revealed an almost complete absorption of the linen strands used at the first operation, whereas the strands of the second operation were only slight absorbed. The report of the pathologist, Dr. F. M. Jeffries, regarding the condition of the artificial canals in the temporal muscle and fascia and in the subcutaneous tissues of the scalp showed that the linen strands brought out through the temporal muscle and temporal fascia at the first operation were almost entirely absorbed, being surrounded by numerous giant cells embedded in proliferative structures rich in bloodvessels and exudative cells. As this was a case of external hydrocephalus no linen strands had been inserted in the ventricles; it will therefore be necessary for us to wait until an examination of such a brain can be made—that is, a case of internal hydrocephalus—and at least six months after the linen strands have been placed in the ventricle in order to ascertain whether their artificial canals will remain as permanent patent channels of exit for the cerebrospinal fluid by

[4] This experimental work will be reported in detail later.

being lined with endothelial cells or not. The fact, however, that the children operated upon have improved and are still improving is of such significance to warrant the assumption that at least the artificial canals in the cerebral cortex are still patent.

With the exception of 6 of the total 28 children living after this operation of drainage, all of them have improved and are still improving; 5 of them have improved mentally and physically in every way, all of these children having been operated within one year after birth; 7 of the patients unable to walk before the operation are now walking, although with difficulty. The different stages of papillo-edema and choking of the optic disks producing a secondary optic atrophy and the visual impairment in these patients have been improved in each case unless a complete secondary optic atrophy had already occured.

Naturally, sufficient time has not yet elapsed to permit an opinion regarding the permanency of this improvement, and whether any of the younger patients will be normal and remain normal; but I do feel that the operative method here used does offer a chance of improvement to a large number of patients formerly considered hopeless; if a definite improvement can be obtained in the older children, then surely an earlier operation in the younger children when the condition is first observed and before the brain has been permanently damaged, should make a more hopeful prognosis possible. I am deeply indebted to Drs. McHenry and Hunt for their assistance; also to Dr. Lott for the apparatus devised by him to insert the linen strands into the ventricle; a description of it and the technic will be described in detail later.

EFFECT OF NUCLEIN INJECTION UPON THE LEUKOCYTES OF DOGS.

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and

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Philadelphia.

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The result of work upon the effect of nuclein in experimental animals has not been uniform, probably because under this name both the acid and its sodium salt have been employed and no standardization has been attempted. In approaching this subject, we determined to employ the product accepted by the American

Medical Association, nucleinic acid or its sodium salt, and to use the phosphorus percentage as our guide.

In counting blood cells three pipettes were prepared for each count, three chambers counted of each pipette, and the number of leukocytes calculated from the average. Differential counts were made of 400 cells in each case.

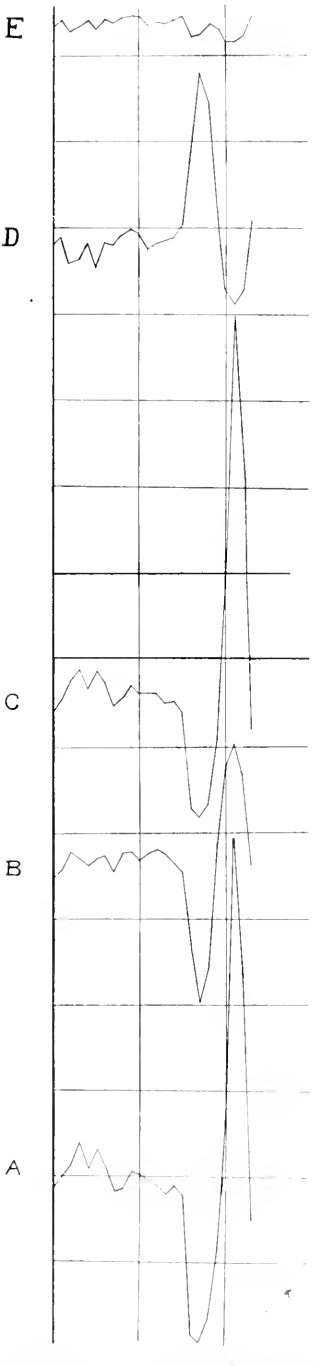
Counts were made immediately before the injection, and after the lapse of $\frac{1}{2}$ hour, 1 hour, 2 hours, 4 hours, $7\frac{1}{2}$ hours, 24 hours, 48 hours, 72 hours, and in some cases 96 hours after the injection. The effect of repeated puncturing of the dog's nose was controlled by taking counts on several untreated dogs. The effect of the injection of the menstruum in which the nuclein was to be administered was controlled by making counts after the intravenous and subcutaneous injection of physiological salt solution and 15 per cent. alcohol. The sodium nucleinate solution was prepared in 15 per cent. alcohol and physiological saline, in every case immediately before injection, and an amount of nuclein equivalent to 0.5 mg. phosphorus per kilo of dog weight was injected subcutaneously and intravenously in solution, 1 c.c. of which was equivalent to 1 mg. of phosphorus. The dog with which most work was done was a female of the fox terrier type, varying in weight from 7 kilos to 10 kilos in five months; of 24 counts taken in that time without treatment, the lowest was 7000 and the highest 13,000.

The injection of alcohol or of physiological salt solution, either intravenously or subcutaneously, was followed by no variation that did not fall within normal limits.

After the injection of sodium nucleinate, whether in 15 per cent. alcohol or physiological salt solution, whether subcutaneously or intravenously, there is a primary fall in the whole number of peripherally circulating leukocytes. This reaches its lowest point between the first and second hour, after which it starts to rise. The count is back to normal between four and seven hours, but the rise continues, until at the end of twenty-four hours the highest point is reached. From the twenty-fourth hour there is a gradual decline, the normal being reached between the seventy-second and ninety-sixth hour. In every experiment the curve greatly exceeded any figure for a similar period without treatment. The results of intravenous and subcutaneous injections are comparable, the clearness of the results, however, being greater by the former method.

Renner was able to raise the leukocytes 452 per cent. in his highest human case. Our greatest increase in the dog has been 290 per cent. of the original count.

The differential counts show after nuclein injection a relative and absolute decrease of polymorphonuclear neutrophiles, followed by a rise. This fall and rise of the polynuclear is largely responsible for the fall and rise of the whole count. Accompanying this curve of the polynuclears there is a similar downward and upward course



The curves are drawn to scale. *A*, variations in total number of white blood cells; *B*, variations in the per cent. of polymorphonuclear neutrophiles; *C*, variations in the number of polymorphonuclear neutrophiles; *D*, variations in the per cent. of small lymphocytes; *E*, variations in the number of small lymphocytes.

of the small lymphocytes, but it is of much less marked degree and more variable in its percentage; so much so, indeed, that no definite curve can be platted which will be followed in every experiment. In every case, however, the percentage of lymphocytes rises as the percentage of the polynuclears falls, and falls as it rises. This in itself shows that the gross variations in the total count must be due to polynuclear fall and rise. We are not now prepared to discuss the variations of the other leukocytes.

In a dog with an orginal leukocytosis and an eosinophilia the effect of the nuclein was the same as in the case of dogs with a normal blood picture.

In order to see if daily or twice daily injections of nuclein in 15 per cent. alcohol subcutaneously in quantities equivalent to 0.1 mg. of phosphorus per kilo would increase the leukocytes continuously and maintain them at a high level, a dog was given this treatment. There was a trifling rise of the whole number and of the percentage (therefore also the absolute number) of polynuclears. There was no continued rise, and the increase was irregular. This line of experimentation will be pursued further.

The Arneth formula in dogs is about as follows: 18, 40, 30, 7, 3. The injection of alcohol and saline has no appreciable effect upon it. Following an injection of nuclein, especially when given into the vein, there is a great relative and numerical increase of Type 1, cells with a single nucleus, amounting in one case to 52 per cent. of the polynuclears, while Type 2 remains about as normal and Types 3, 4, and 5 decrease. The rise of Type 1 seems to reach a high point in four hours corresponding to the time at which the leukocytes are on the increase and remains during the period in which the polynuclears are rising. Types 3 and 4 experience a fall roughly corresponding to the rise of Type 1, and later, corresponding again to the fall of Type 1, show a distinct increase, this arriving about the time that the leukocytes have resumed their usual numbers.

Nucleated reds have been encountered very occasionally in normal blood. After the injection of nuclein subcutaneously they are slightly increased, but when the substance is given into the vein they are increased quite markedly, in one case rising to eight times the number before injection. This rise appears during the time the leukocytes are falling. From a few observations it does not seem that there is any reduction in the number of red blood cells.

In 4 cases general toxic effects were noted after the intravenous injection of nuclein. The dogs became very restless for a few minutes, then lay quiet but trembling on the floor. After one and a half hours there was vomiting of a frothy yellow material, which vomiting was repeated throughout the day. On one occasion there were no general toxic symptoms.

Tentative conclusions from this work are that after nuclein injec-

tion there is a reduction in the circulating peripheral leukocytes, chiefly of the polymorphonuclears, and to a much less degree of the small lymphocytes, followed by a rise in both, but very largely of the polynuclears, even to 95 per cent. of the whole count. The total leukocyte count in dogs may be increased 290 per cent. in twenty-four hours. Repeated small doses of nuclein do not cause and maintain a high tide of leukocytosis. There seems to be destruction of polynuclears because of their great decrease, and the relative and absolute increase of young forms on the left side of Arneth's formula. The appearance of these young forms and of an increase in nucleated reds speaks for an increased activity of the bone marrow, therefore a stimulation of the tissue, but whether by the nuclein injected, as a response to the paucity of circulating white cells, or by excitation by the detritus of destroyed leukocytes we have not yet determined.

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THE LIMITS OF BLEEDING CONSIDERED FROM THE CLINICAL STANDPOINT.[1]

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There has been a tendency of late to overemphasize the importance of blood transfusion methods when in reality there is greater need for a more thorough understanding by the medical profession

[1] Read before the Semi-annual meeting of the Medico-chirurgical Faculty of Maryland, April 26, 1916.

at large of the indications for this procedure. It may well be that the cross-roads doctor is still unable to carry out a successful transfusion because of the complexity of present-day methods; one might even admit that the final word has not as yet been said on this matter; but the fact remains that for all practical purposes it is possible now for those properly qualified to do a successful transfusion with considerable ease, with absolute certainty and safety, on men, women, children, and infants, and by any one of several different methods. It goes without saying, of course, that to achieve the best results one must be prepared to use that method best suited to the case in hand, since no one device answers equally well in every instance.

If this is granted, then, it behooves the medical profession at large to learn what are the indications for this procedure and to become better acquainted as to the limits of bleeding, knowledge of which I have found to be sadly lacking. Indeed, it would have been strange had there been a wide-spread knowledge of this subject, since there was little to be gained by its intensive study prior to the advent of the practical transfusion. The therapy of anemia in its various grades has always been pretty well understood, and the treatment of actual hemorrhage from different causes has likewise been well recognized; so that heretofore it would have availed one little to study the actual limits of blood loss, with a view to relieving the condition when it got, so to speak, "out of bounds." The means of relief at one's command were insufficient. But times have changed. It is now possible to introduce fresh blood, literally at a moment's notice, into a circulation depleted by accident or disease. The only question to be determined is, When has the limit of bleeding been reached; and by limit of bleeding I refer to progressive anemia of any sort, from any cause.

The more I see of hemorrhage and anemia in general the more am I convinced of the utter futility of having a specific rule by which to be governed. Each case is a study unto itself, each individual represents an entity, each must be judged from all angles if one is to faithfully discharge his duties; and experience alone is the final great teacher in this as in all other phases of medicine. Yet one must have some tentative plans by which to be guided, and there are, after all, certain fundamental features which are true to a degree in all cases, and that are, if not regarded too literally, to be depended on. For instance, a sudden loss of blood is a much more serious matter than a gradual depletion. I once transfused a boy of about seven years who had had a progressive anemia of some months' standing of such grade that at the time of transfusion his hemoglobin was too low to register on any of the instruments commonly used for such work. Yet he was not in any immediate danger at the time of transfusion. And not long ago I transfused a woman whose hemoglobin actually registered 40 at the time of operation—

a reading that, under ordinary circumstances, is well within the limits of safety—yet this patient was in such a precarious state from sudden loss of blood, consequent upon a volcanic gastric ulcer, that the transfusion was terribly hurried.

A rapidly falling blood-pressure is always a warning of value, although it must be remembered that nausea of the slightest degree will send the pressure down. Pallor, the clammy, sweaty skin, the anxious countenance, are all danger signals that occur to you at once, and air-hunger when present is always of true diagnostic import.

In cases of severe hemorrhage—it matters not what the cause—a good working rule is to transfuse if the blood-pressure falls as low as 70 mm. of mercury, since life is hardly possible with anything below this level. But even in these cases the rule must be somewhat elastic because one can never tell when the pressure is going to rise. In some instances if the physician or surgeon in charge of the case has not taken the steps usual in emergency cases, such as salt infusions, etc., it may be wise to delay until these can be instituted, preparations for transfusion being made in the interval. If no appreciable results occur within one hour the case is usually hopeless unless new blood is introduced, and procrastination at this stage of the game is a fearfully dangerous plan, as the following story illustrates: Not many months ago I was called to see a woman who had had a placenta previa, and had been delivered in the manner usual for such conditions, a fair amount of blood being lost, though not nearly enough, according to the obstetrician in charge, to have caused the profound shock that ensued. The usual measures to combat such a condition were at once instituted and had been carried out before I reached the hospital. When I first saw her the patient was in a semiconscious condition, breathing was very shallow, and her pressure was around 70. Those in charge of the case, however, felt that in the fifteen minutes prior to my coming there had been a slight improvement, and the blood-pressure readings appeared to corroborate this, so that it seemed as if the condition might be one of pure shock, and that, if let alone, the patient might recover without transfusion. We waited just a half hour, but during those thirty minutes we lost our only chance, for suddenly the pressure dropped still further, the patient became absolutely unconscious, and died just as the transfusion was started. It is impossible for me to express the disgust I felt for my own judgment and my chagrin at the loss of that case. After years of study and after an experience varied and unique in hemorrhagic conditions I had begun to believe that I could really size up the situation in such a case. And the worst of it was that I had formulated this arbitrary rule of transfusion at 70 mm. pressure over two years prior to this case, and had never before broken it. Nowadays, I not only adhere to this rule religiously but go even a step farther—

when in doubt, my advice is to transfuse. It not infrequently happens that the pressure has not fallen to 70 mm., and never does reach that level, but the other features of the case are such as to render delay hazardous. Only once in my experience has a case been lost by transfusion; three have now definitely been lost by not transfusing, and in all three the opportunity was offered but not grasped. In fairness to myself, however, I will say that I advised against delay in two out of the three. In the case lost by transfusion the emergency was so great that time was lacking to carry out the usual hemolytic tests, and, as luck had it, the blood used was incompatible, hemolysis occurred, and the patient succumbed one week after the operation. This is the only instance of fatal hemolysis in my entire experience.

Curiously enough, the blood picture itself is of little avail in severe accidental hemorrhage. I once transfused a woman who was apparently exsanguinated from a gastric hemorrhage, yet her hemoglobin was around 50 per cent., and her red cells were over 2,000,000—figures well within the limits of safety. Even in cases of actual air-hunger, blood counts alone do not indicate the dire need for fresh blood. In fact, so constantly has this state of affairs been found in cases of this sort that this feature is now entirely ignored—I do not even go to the trouble to determine the hemoglobin or the red count. The explanation of this seeming paradox is that a sudden, terrific loss of blood apparently gives rise to a tightening up at first of the vascular apparatus, a narrowing of the vessel lumen, thus causing a concentration of the blood remaining in the peripheral system and at the same time preserving a blood-pressure sufficient to sustain life. The true anemia does not become apparent until later on, when the vessels have relaxed and taken up a renewed supply of plasma with the resultant blood dilution. It is, therefore, not infrequently an extremely difficult matter to determine the actual limits of bleeding. Cases must be judged in the aggregate, after a careful consideration of all features, and even then a positive answer is not always forthcoming.

I am not clear in my own mind as to the proper definition of so-called "shock," and it appears that many others have a similar hazy conception; but there is, without doubt, a certain something, commonly called shock, which complicates many of these cases. Not once but dozens of times the story has been that a comparatively slight loss of blood occurred—stories cited by men whose honesty was not to be questioned, whose keenness of observation is well recognized—still the patient looked as if there was not a drop left in the body, and blood-pressure readings were difficult to obtain because of a fluttering pulse. One such case followed a hip-joint manipulation by the open method; a fat embolus did not explain the condition found nor did the anesthesia, yet the patient died before transfusion could be instituted. Another

instance followed a dilatation of the cervix and removal of a child by version, giving rise to a fearful condition not explained by loss of blood alone. Prompt introduction of blood apparently righted the lost equilibrium. Is this condition due to anemia of the brain, or is it really connected with Crile's kinetic theory? I confess it to be beyond my ken. Having constantly to reckon with this phase of hemorrhagic conditions—for shock is nearly always associated with bleeding in the cases I am called upon to judge—I find it at the same time enigmatical and terrifying, for it introduces an unknown factor into conditions trying enough without it.

But before dismissing the subject of accidental blood loss, a few words might be in order concerning the use and abuse of drugs and salt solution in the treatment of these conditions. It is an awful thing to sit still and watch a man bleed to death, without so much as a decent attempt to save him. We all know that. It upsets everyone, makes everybody nervous, and this surely is the explanation of the hurry and bustle of an operating room in which the unexpected has happened, the delivery room in which the bleeding has been too great. But we might as well realize the truth; perhaps a proper realization will bring us to our senses. Drugs are of little aid in acute bleeding, morphin, judiciously given, excepted. Never have I seen the slightest benefit from strychnin, nor have nitroglycerin nor atropin been of much service. Digitalis and strophanthin may possibly momentarily support a faltering heart, but it is not the heart that is at fault. In the severe obstetrical bleedings that I have seen, even ergot and pituitrin have been of doubtful value. Yet the practice of giving one drug after the other, hypodermic on top of hypodermic, is still in vogue—so much so that it would be astonishing did I but enumerate the various "stimulants" given to one rather recent case. It is human nature to try to help, but drug therapy in acute bleeding is misdirected aid.

Personally, I think a quarter of a grain of morphin seems to be indicated at the start of any hemorrhage to quiet any restlessness; after that the doses had better be smaller, because of the depressant effect of this drug on respiration and blood-pressure. Measures to stop the bleeding should be instituted immediately, and the body should be kept as warm as possible, the foot of the bed elevated, the limbs bandaged, the patient kept quiet, and water given *ad libitum*. And by water, I mean liquids of any and all sorts, by mouth, per rectum, subcutaneous infusion, intravenously, coffee, tea, water, salt solution, ice—anything at all that will quench the intolerable thirst and keep up the bulk of the circulating medium—all within reason. And right here, perhaps, I may be permitted to sound a note of warning—too much has been expected of salt solution—far too much. The custom of giving salt solution (or water) per rectum after an operation of any magnitude is a good one, and the salt infusion in cases of bleeding is also good, as is at times

intravenous salt—all within reason. But it is ridiculous in the extreme to keep filling a patient full of salt solution just because a great quantity of blood has been lost. Salt solution will not turn into blood—yet it is all but expected to do so.

If I have seen one I have seen a dozen patients actually waterlogged by salt solution—and with no improvement whatsoever. It never seems to occur to some men that a heart can be overdistended, that the blood can be made too dilute, that if 1000 c.c. or 1500 c.c. of salt do no good, a greater amount will be equally valueless. But time and time again have I seen infusions repeated after 2000 c.c. of salt have been given without any benefit at all. Everyone knows it is proper to give salt solution in cases of blood loss, but very few stop to consider how much ought to be given. Some three years ago I was asked to see a gentleman, aged sixty-five years, who had had a suprapubic prostatectomy done. He went off the table in very good shape, but a few hours later began to bleed, and had to be repacked. Even this did not stop the ooze. So about four or five hours after the operation he was taken to the operating room and thoroughly packed under light gas anesthesia. Rather shocked from this procedure, but still in fair shape, he was returned to his bed and readily took up 2000 c.c. of salt solution. In spite of this he gradually became weaker, and finally developed a Cheyne-Stokes form of respiration. When I saw him his blood-pressure was around 70 and he was in a semiconscious condition. Those in charge wished to delay because he was taking up the salt so well, but gave in after a brief argument. On incising his arm for a direct transfusion, not a drop of blood flowed from his tissues, but salt solution flowed very freely. The introduction of a few hundred cubic centimeters of blood from his son saved his life; and curiously enough the Cheyne-Stokes form of respiration disappeared while the blood was actually flowing into him.

It should be generally understood that if the bleeding has not been too great a few hundred cubic centimeters of salt are all that is needed to tide a patient over. In cases of very severe hemorrhage the amount might be increased a bit, but if 1200 c.c. do not steady a falling blood-pressure or cause a slight rise its introduction had better be discontinued. Even when there has been a rise the greatest caution must be exercised, for be it remembered that in these desperate conditions salt will frequently cause a rise in blood-pressure, but will not sustain it. When the bleeding has been excessive a transfusion is indicated, because it has been conclusively shown that blood alone can raise a pressure and sustain it. Salt solution has no sustaining power *per se*, and when the fall comes after a rise from this means it usually portends the end, for added salt solution is useless. It never raises a pressure twice!

One would think that little need be said concerning the limits of bleeding in the more gradual forms of blood loss, but experience

teaches otherwise. Not many weeks ago, toward 5 o'clock one afternoon, I was asked to see a little girl with a view to possible transfusion. On arriving at the hospital, and before going up to see the patient, the story was told that a slow nasal bleeding had been in progress for six weeks or more and that all measures of relief had been utterly futile. Her condition had not seemed alarming until some twenty-four hours previous, when signs of collapse appeared, which were combated by a salt infusion. As no permanent relief was afforded by this means, transfusion of blood was thought of, but when I saw the patient it was apparent that a transfusion was not for her—she was actually dying! Nor would I set these cases down as instances of sheer stupidity or ignorance, because the physicians responsible were well up in their general work and desired to do all in their power for their patients. The unfortunate feature was that, being unaccustomed to deal with intractable bleedings, they were uniformed as to the limits beyond which one dare not go without introducing fresh blood. It is quite possible, too, that some of them did not know that intravenous whole blood will almost always cause a cessation of a gradual ooze from most any cause—they failed to take advantage of their opportunities and their patients paid the penalty.

It should be understood that in cases of chronic bleeding the coagulation apparatus tends to become deranged, and the longer the seepage continues the less liable is spontaneous cessation to occur. And the curious feature is that in many of the worst of these cases, the coagulation time of the blood outside the body is but little delayed. I have no explanation for this phenomenon, but can vouch for its accuracy by repeated tests. Therefore, in cases of gradual bleeding from any cause too much must not be left to nature. Depletions from sloughing fibroids should never be permitted to progress beyond the safe operative stage; yet I have seen it done! No case of obscure internal bleeding in this enlightened day should progress so far as to need a transfusion; yet I have seen it done! No case of actual hemophilia should be allowed to go so far that the patient is exsanguinated before resorting to blood introduction; yet I have seen that done! The slightest bleeding in the newborn infant should be a signal to prepare for a transfusion; but is this done? By no means. Only a few days ago I was requested to see a two-weeks-old babe that had had a slight vaginal bleeding a day or two after birth, a few purpural spots later on, and finally an umbilical hemorrhage that resulted in death just a few moments after it was brought to the hospital for transfusion!

Let me emphasize that bleeding is a phenomenon of the gravest import. Little does one realize the vast number of lives lost yearly from this cause, since no statistics have ever been compiled on the subject. I had no idea of its consequences until some time after starting in transfusion work, but as the years roll by my list of cases

designated by the fateful words "too late" grows perceptibly, until now I take it as a matter of course that not an inconsiderable percentage of the cases I am called to see are beyond help simply because of an insufficient knowledge concerning the limits of bleeding. In fact, it was a study of these "too late" cases that prompted me to take up the subject in the hope that a renewed interest might be awakened.

Even the chronic anemias are, from my view-point, permitted to progress entirely too far. I ask why is it necessary to delay transfusion in cases of pernicious anemia until the victim has a hemoglobin so low that an accurate reading is extremely difficult —15, 12, even 10 per cent.—and the patient is pale as death and so weak that transfusion is an extremely dangerous undertaking? Fresh blood does not cure these cases, that I well know, but in general it will cause a remission after all other measures have failed. Then why not transfuse, if transfuse at all, before the very bottom has been reached? Some may say that one can never tell when drug therapy will start the rise? If so, I agree with them, but in my experience after drugs have caused one or two remissions a continuously falling hemoglobin under this therapy is a danger signal, and when the hemoglobin reaches say 30 per cent., why not introduce new blood and give the drugs a bit more to work on?

The same thing may be said of the indefinite undiagnosed anemias, some of which are permanently cured by transfusion. And the intestinal bleedings from ulcers, duodenal, gastric, may be placed in the same category. The convalescence of many of these patients could be materially shortened by the introduction of whole blood. Why compel them to start from the depths and rebuild entirely when one knows it to be so difficult and tedious when, by repeated demands, the blood-forming organs have been strained to the breaking point? And since many of these individuals have difficulty in getting beyond a certain point in their rebuilding process, it has often occurred to me that the impetus resulting from a medium-sized transfusion at this point might be a stimulus of inestimable value in healing the ulcer and finally regaining complete strength and health, a point that has hitherto had but passing consideration.

And how often are surgeons called upon to operate on patients whose strength has been sapped by some chronic wasting process that is only another form of bleeding? Deaths from such operations are not infrequent, yet poor surgical risks of this sort can be turned into good operative risks without the slightest difficulty by a transfusion prior to operation, or, as I have frequently done, during actual operation. One case in particular, a little out of the ordinary perhaps, but extremely instructive, may be cited: A man came in suffering with a double pus kidney. He stood one operation fairly well, but failed to respond after drainage of the other side. For days all measures of relief were tried, but he continued to slip away,

and his last kidney wound became a foul, sloughing cesspool, while his temperature was continually mounting. A blood transfusion changed this individual from one absolutely lost to a man of hope; his temperature dropped, the wound in his side gradually cleared, healthy granulations sprang up, and he left the hospital in good shape not many weeks later. And I maintain that is a triumph of the most fundamental character.

In conclusion, I would urge that henceforth transfusion be not regarded entirely as a measure of last resort—food for the reporters by spectacular stories of the dead brought back to life. A more thoughtful attitude concerning blood loss from any cause is greatly to be desired, and the phenomena accompanying bleedings of all magnitudes should be carefully noted and studied, with the view to improving the general knowledge of such matters. Furthermore, a partial revision of the existing ideas of combating hemorrhage and the condition commonly known as shock may possibly be of material advantage in view of the fact that transfusion may be done so readily at the present time. But above all, surgeons and physicians should learn to recognize the limits of bleeding and to act promptly. In the acute hemorrhages, according to my experience, the safest guide is the blood-pressure; in the chronic bleedings and the anemias it is the hemoglobin; but one must never lose sight of the fact that at times all signs fail, and there remains naught for guidance but experience and judgment. Under these circumstances my advice is, "When in doubt, transfuse!"

THE MAIN FACTORS AFFECTING THE INTENSITY OF SOUNDS AS THEY PASS FROM THE INTERIOR OF THE LUNGS TO THE PERIPHERY OF THE CHEST.

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The intensity of sound as it passes between two places may vary in one of three ways: It may become intensified, it may remain constant, or it may be diminished. In these general features sound presents certain resemblances to light. Factors operating to increase sounds between the interior of the bronchi and the periphery of the chest are little understood and are probably of very minor importance, as far as the mere intensity of audible sounds is concerned. Factors concerned in maintaining the original intensity of sounds are found particularly within the bronchi, which act much

as speaking tubes in preventing, through limitation of diffusion, the weakening of the sounds coming from the upper respiratory tract, while at the same time the bronchi carry the sounds deeply within the lungs, thus preserving a good deal of their original intensity. The bronchi, however, provided they are patulous, and not too far retracted toward the root of the lung, exert their influences on the sounds within them under both normal and pathological conditions, so that to a large extent our interest centres on the sounds *after they have escaped from within the bronchi*. It is not, however, with an increase in sounds, or their retention, that we are chiefly concerned, but with those factors tending to effect a diminution in the intensity of sounds in the chest.

The Diminution of Sounds. The diminution of sounds in different clinical conditions as they pass from the interior of the bronchi to the periphery of the chest, depends chiefly on one or both of two factors: *the diffusion of sounds* and *the reflection of sounds*.

The Diffusion of Sounds. By diffusion is meant a spreading out of the sound, a dilution of the sound energy. If a sound originates at a point, and, owing to the non-existence of any obstructions, spreads out equally in all directions, the intensity of the sound will be the same on all points of the surface of a sphere whose centre is at the point of origin of the sound. At the surface of a second sphere, double the area of the first, and concentric to the same point of sound origin, the vibration energy, per unit of area, and hence the intensity, is halved. This is a deduction from the so-called inverse square law of acoustics, which tells us that, in a medium in which the absorption of energy is small enough to be neglected, and which is extended enough (infinite) so that the complications introduced by boundaries may be disregarded, the intensity of a sound varies inversely as the square of its distance from the source. The importance of the factor of diffusion of sound in diminishing the intensity of sounds as they approach the surface of the chest has, for the most part, been understood in only a very general way, and the great relative importance of this factor in certain clinical conditions has been largely overlooked. Thus, the main factor in determining the diminution of vocal resonance in pleural effusion as contrasted with the normal lung, is diffusion.

The Reflection of Sounds. The reflection of sounds is a form of sound obstruction, and is as different from the diffusion of sound as the reflection of light is from the diffusion of light. Of course we are now speaking of reflection as it interferes with the transmission of sounds on their way to the hearer who is situated distal to the point of reflection, for reflection may intensify sounds by actually focussing them to a smaller area. In the chest we look for factors reducing sounds (exclusive of diffusion) either within the different individual media encountered, or at the junction of different media, that is, where different media occur in combination.

The Different Individual Media Concerned. All the individual media with which we are concerned may be divided into three groups: (1) the solids, or, better, the gels, (2) the fluids, and (3) the gases. It is very easy to show that *each of these individual media by itself offers but little obstruction to the passage of sound through it, and that whatever proportion of sound is lost in its passage through these individual media is due to diffusion.* In the de-intesification of sounds on their way to the periphery of the chest, no differences in the conductive properties of any of these media, solids (or gels), fluids and gases, have been determined by the stethoscope, and therefore are not of present concern to us.

Different Media in Combination. Apart from diffusion the chief factor in diminishing sounds passing through the chest is the reflection of sounds occurring at the junction of certain of the above mentioned media. *Comparatively little sound is lost in its passage between fluid and tissue (or solid), because their densities are not greatly different and they are both highly elastic. But between air and tissue or air and fluid, provided the body of tissue or fluid is not too attenuated, a very marked "break" occurs, because of the vast differences in density of the adjoining media.* As far, then, as different media in the chest affect sound intensity by their combination, they may be roughly reduced to two: a medium of air and a medium free from air.

To summarize what has been said about the diminution of sound in the chest, we are dealing chiefly with two factors—diffusion and reflection—the former occurring fairly constantly, the latter for the most part requiring the presence of air and taking place mainly at the junction of air with either solid (tissue, gel), or fluid. Or, to put it in another way, there is very little diminution of sound in the absence of air, except that due to diffusion, provided the bronchi are patulous and not reduced in size.

In speaking of the combination of tissue and air as offering an obstruction to the passage of sounds, the degree of obstruction will depend on the thickness of the tissue adjacent to the air. Thus, much more sound is lost when the vibrations are passing from air to chest wall, than from air in one of the vesicles in the lung to the delicate enveloping membranous wall. The fact that sounds pass though the normal lung with as little loss as they do, is largely because each delicate membrane individually offers relatively very little obstruction. *More obstruction occurs when these membranes are tense than when relaxed, the greater tenseness of the membranes in the former case effecting a greater degree of reflection of the vibrations.* The result is the well known clinical fact, that the normal lung in the normally distended state impedes the transmission of sound more than when in a state of collapse. *A great difference in transmissability can be shown to exist when the sounds traverse equal distances in distended and relaxed lungs.*

While the solid tissues of the lung (normal and diseased), and of

the chest wall in the living body contain a large proportion of fluid in the form of lymph and blood, this mixture of two different media, fluid and tissue, does not materially reflect or obstruct the passage of sounds, for the reason given, that the densities of tissue (normal and pathological) and fluid are relatively alike.

The purely solid portions of the tissues we are considering are made up chiefly of soft cellular substance, which, to a large extent at least, is physically allied to gelatin, and belongs to the group of gels, substances which it is well to bear in mind are very different physically from such solid materials as wood and metal. These gels, though potentially capable of yielding a large proportion of fluid, do not actually contain it, just as gelatin, though capable of yielding much water, does not do so as long as it is in the state of gelatin.

Absorption, Resonance and Interference of Sounds. Besides the main factors of diffusion and reflection of sounds there are other factors affecting the intensity of sounds within the chest, but their activities, what little we know about them, appear to be much less influential. On the quality of sounds, however, at least in the case of resonance, their effect may be very marked. By *absorption* is meant the annihilation of sound energy as such, and its conversion into other forms of energy, such as heat, which may not be appreciated by the ear. It is a factor concerned in the diminution of sound intensity quite distinct from diffusion, though at times confused with it. Absorption by different media apparently plays a very small part in the reduction of sound intensity in the chest. *Resonance* acts particularly by affecting sounds of a certain pitch, and as the chest sounds familiar to us are compounded of many different kinds of individual sounds, resonance usually exerts its influence only on a limited number of these individual sounds. Certain elements in the original sound may be diminished through *interference*, that is, the superimposition of sound waves upon each other.

The Size of the Bronchi as a Factor in Determining the Intensity of the Vocal Resonance. When a bronchus, or a group of bronchi, such as we find in the bronchial tree of one lung, become reduced in size, the total amount of sound energy coming from the upper respiratory tract and being admitted to these bronchi, is less than when the bronchi possessed their original larger capacity. How much of an effect this decrease in the bronchial capacity may exert upon the vocal resonance requires further investigation. This factor would have a particularly favorable opportunity to operate when the whole lung is much reduced in size, as may occur in pleural effusion or pneumothorax. Braune and Stahel[1] have shown that

[1] Ueber des Verhältniss der Lungen, als zu ventilirender Lufträume, zu den Bronchien, als luftzuleitende Röhren, Arch. f. Anat. u. Physiol., 1886, Anat. Abtheilung, S. 5.

the diameter of a bronchus usually depends in part upon the amount of air in the lung, and it seems quite possible that in chronic affections of the lung and pleura the bronchial capacity might become sufficiently reduced to appreciably affect the vocal resonance. The explanation for the greater vocal resonance often encountered normally over the right lung, may rest partly on the fact that the right lung is larger than the left, which necessitates a larger total intrabronchial capacity on the right side, which permits the entrance of a larger amount of sound energy into this side. (The ratio of the diameters of the right and left main bronchi in the normal individual, according to Braune and Stahel, is about 4 to 3, approximately the same ratio that they obtained for the respective weights of the lungs on the corresponding sides.)

The Origin of the Sounds Involved. It is to be recalled that the spoken voice sounds, bronchial breathing, and whispering pectoriloquy arise in the upper respiratory tract, so that the source of these sounds is identical, however variable may be the conditions in the lungs, and different intensities in different parts of the external chest surface must be due to factors operating distal to the source of these sounds. On the other hand, variations in intensity of the vesicular breath sounds, at least of the inspiratory ones, sounds which arise within the lungs, may be due in whole or in part to differences in intensity at the site of production of these sounds. Thus, in pleural effusion, even if slight, the vesicular murmur may be weakened because there is not proper expansion of the vesicular structure to produce sounds of normal intensity.

The Relative Importance of Different Portions of the Respiratory Passages below the Larynx as Direct Sources of the Vocal Resonance. While the trachea and bronchi resemble speaking tubes to the extent that they transmit within their interior sounds coming from the upper part of the respiratory tract toward peripheral portions of the lungs, the walls of the tracheobronchial tree are, all along the route, taking up a certain amount of the sound present within these air passages. Some of the vibrations entering these walls are never perceived by the auscultator, and, in the case of the normal lung, the vocal resonance over most of the chest is due entirely or largely to vibrations escaping from the smaller bronchi. Under these conditions the trachea and larger bronchi serve only as carriers of sound from the upper respiratory tract to the smaller bronchi. The normal right apex, according to Fetterolf,[2] receives some audible vibrations that have come directly from the trachea without having had to pass through the bronchi. In pneumonia it has been shown by Mason[3] that the voice

[2] The Anatomic Explanation of the Greater Amount of Vocal Fremitus and Vocal Resonance Normally Found at the Apex of the right Lung, Archives of Internal Medicine, February, 1909.

[3] American Journal of Diseases of Children, March, 1916.

and breath sounds become much altered when a peripherally situated consolidation, previously separated from the large bronchi by an area of normal lung tissue, by extension centrally, finally comes in direct contact with these large bronchi. The large bronchi furnish some of the sound when the lung assumes the fetal type following the disappearance of air from within the alveoli. The trachea itself may be a direct source of sound when the upper part of the lung is solid, or when the upper portion of the pleural cavity is filled with air or fluid, the pulmonary apex being free from adhesions and retracted toward the root of the lung.

While fully recognizing the limitations of the explanations offered for various auscultatory findings obtained over the lungs, we believe that the application of the simple principles just presented to certain clinical conditions can frequently be determined to a considerable

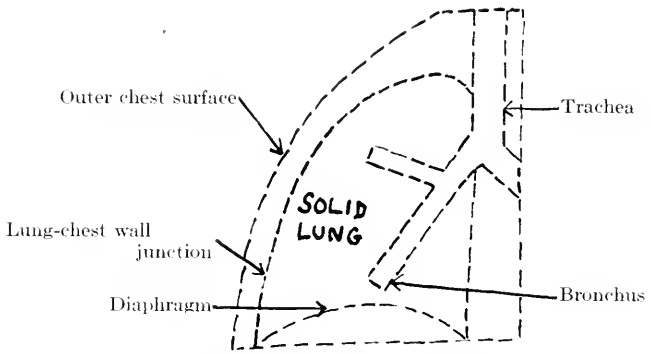

FIG. 1.—Solid lung. No special reflection, the entire distance between bronchial wall and outer chest surface. Diffusion an important but not a special factor. More sound retained within the bronchi, at least, the small ones, than normally. Vocal resonance increased. Bronchi in diagram represent small as well as large bronchi.

extent. Six of these conditions will receive brief attention: solidified lung, normal lung in a state of normal distention, collapsed but otherwise normal lung, pleural effusion with diminished vocal resonance, pleural effusion with increased vocal resonance, and pneumothorax.

Solid Lung. This is the simplest clinical condition we have to study. In tracing the sounds from within the bronchi through the solid lung to the periphery of the chest we find the factor of diffusion of sound everywhere operative. The activities of this factor are very much limited within the bronchi because the bronchial walls to a great extent reflect the vibrations back into the interior of the bronchi, this reflective action in the smaller bronchi being even more powerful when the lung is solid than when it is normal. Once the vibrations have entered the bronchial walls, however, their further course is pursued entirely through tissue with

its associated fluids, the solid lung and chest wall forming practically a single good conducting medium which offers very little obstruction to the passage of the vibrations, so that *nearly all the sound intensity that is lost en route from bronchus to chest periphery is due to diffusion.* In no other common clinical condition do we find so little tendency to the reduction of sounds from reflection as when dealing with a solid lung. And even the degree of diffusion is not greater than that ordinarily encountered. The voice sounds are, therefore, relatively loud, or, as we usually express it, are increased in intensity over a solid lung. In addition the weaker sounds produced in the upper respiratory tract, bronchial breathing and whispering pectoriloquy, become audible at the chest surface, while the normal breath sounds disappear because they are not produced.

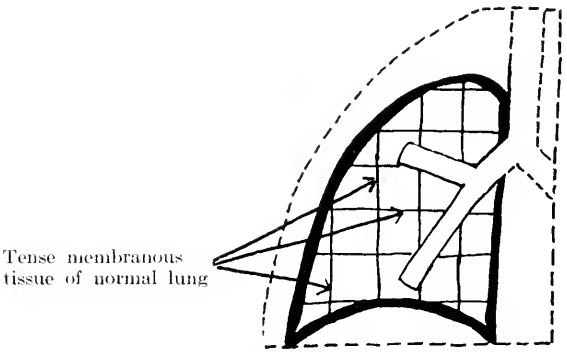

FIG. 2.—Normal lung. Special reflection (indicated by continuous lines), first, at junction of the air in the lung with the chest wall; second, at junction of tense membranous tissues of lung with air in the vesicles, and, possibly to some extent; third, at junction of bronchi with air in adjacent vesicles. Diffusion much as in the case of solid lung. Vocal resonance normal. Bronchi in diagram represent small as well as large bronchi.

The Normal Lung Normally Distended. The conditions present in a chest containing normal lung in its normal state of tension offer a marked contrast to those occurring when the lung becomes solidified. Such a lung, unlike the solid lung, does not exhibit a single good conducting medium free from air between bronchial wall and chest wall. Instead, we find air associated in a very peculiar way with the delicate membranous tissues of the pulmonary parenchyma, these membranes at the same time being under a considerable degree of tension. Sound energy is lost, (1) as the vibrations pass from the bronchial walls to the air in the nearest adjoining vesicles; (2) as the vibrations pass between the air in the vesicles and the tense membranous walls enclosing them, and (3) as the vibrations pass from the air in the vesicles immediately underlying the chest wall to the tissues between these vesicles and

the chest wall, which practically means to the chest wall. *Each such loss of energy is the result of reflection* acting on the vibrations as they pass toward the exterior of the chest. It is not surprising, therefore, with all these places unfavorable to the transmission of sound, that the normal vocal resonance is so much less intense than when the lung is solid. In fact, it is more difficult to explain why the voice sounds are not actually weaker than they are. Two conditions may be mentioned which are relatively favorable to sound transmission when the lung is normal: (1) Sound can more easily escape from within the smaller bronchi to the thin walls of these smaller bronchial tubes of the normal lung than when these tubes become encased in solid tissue. (2) There is some sound conduction even in the thin membranous tissue of the normal lung. The absence of bronchial breathing and whispering pectoriloquy over normal lung is due to the same conditions that make the vocal resonance less than that over solid lung.

Relaxed but Otherwise Normal Lung. Clinically this condition occurs above a pleural effusion and is apparently responsible for the increased vocal resonance frequently found above an effusion. A good deal of the confusion and error that has resulted in the attempt to explain different degrees of intensity in the sounds heard over the chest has been due to a failure to recognize *the different effects on sound transmission occasioned by the normally distended lung and the collapsed lung*, or, as it is frequently termed, the compressed lung. Bullar (1884) was the first one to describe the marked differences in conductivity of these two kinds of lungs, though he offered no explanation for this variation. *The relaxed lung allows vibrations to pass through it with less obstruction or reflection than the distended lung*, for the reason given in speaking of the normally tense lung, that is, *because the relaxed membranes of the collapsed lung are not under tension*, and therefore reflect the vibrations backward to a much less extent than when the same membranes are tense. This principle is well known, and can be readily illustrated by passing sounds into a tube and listening at the far end, when it will be noticed that if a thin piece of rubber membrane (or body tissue) is placed across the lumen of the tube at some point, much less sound gets through to the far end of the tube when this membrane is held taut than when it is completely relaxed. The relaxed lung lets more sound through it than the distended lung even when the area traversed in the two cases is identical. In all respects, *except the degree of tension of the finer tissues*, the relaxed and tense lungs are very much alike as far as sound transmissibility is concerned, when equal distances in the two kinds of lungs are compared.

Pleural Effusion with Diminished or Absent Vocal Resonance. The explanations for this phenomenon when not entirely erroneous have been either obscure or incomplete. The abnormal

conditions encountered in a simple case are the presence of fluid within the pleural cavity, and a more or less relaxed lung. The clinical fact above referred to, that the vocal resonance above a pleural effusion is frequently increased, indicates that the sounds escape from the relaxed lung to adjacent tissue with more intensity than in the normal case. The evidence indicates that the sounds pass between a relaxed lung and fluid with about an equal intensity to that found in the passage of sounds between relaxed lung and tissue. Therefore, in those cases presenting an increase in vocal resonance above an effusion we conclude that the vibrations entering the fluid are louder than those entering the chest wall of an individual with the lung in a normal state. *Any loss of sound, then, (except as noted below), encountered over a pleural effusion, must take place after the vibrations have entered the fluid.* We have already seen

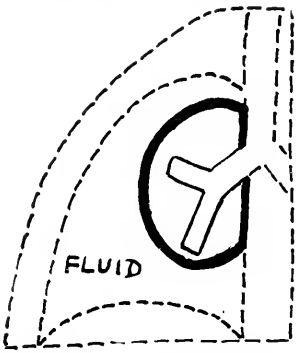

FIG. 3.—Pleural effusion. Lung air-bearing, but membranous tissue relaxed. Special reflection (indicated by heavy continuous line) at lung-fluid junction. Reflection at junction of bronchi with adjacent intravesicular air (indicated by light continuous lines) of questionable importance. Special diffusion between lung and chest wall. Vocal resonance decreased. Bronchi in diagram represent small as well as large bronchi.

that tissue alone, and fluid alone, and even the combination of the two, offer very little impediment to the passage of sounds. *The loss of sound encountered over an effusion may be traced largely to diffusion*, the result of the greater distance occurring between the lung and the chest wall overlying the fluid as compared to the close approximation of the lung to the chest wall under normal conditions when no fluid separates them. The sounds become weak over an effusion for the same reason that they do over the liver, because of diffusion and not because of reflection. When the lung is much reduced in size the diminished vocal resonance may be partly due to the decrease in size and capacity of the bronchi, which allows less sound to enter the lung than normally. When effusion is present the vesicular murmur may be diminished or absent partly because the vesicles are not expanding properly to produce sounds of normal intensity.

Pleural Effusion with Increased Vocal Resonance. The explanations offered to account for an increase in the vocal resonance sometimes met with over a pleural effusion are few and for the most part unsatisfactory. *In some cases this increased vocal resonance is apparently due to the fact that the fluid adjoins a lung which is solid.* The lung may be solid simply from absence of air in the vesicles, as when it assumes the fetal type after prolonged collapse, or it may be solid as a result of inflammatory or other products in the vesicles. It is important that no air should remain in the pulmonary parenchyma. *When a solid lung is separated from the chest wall by fluid there is very little reflection or other form of obstruction to the passage of vibrations on their way to the periphery of the chest, after they have entered the bronchial walls. Neither the tissues (lung and chest wall), nor the fluid, either individually or in*

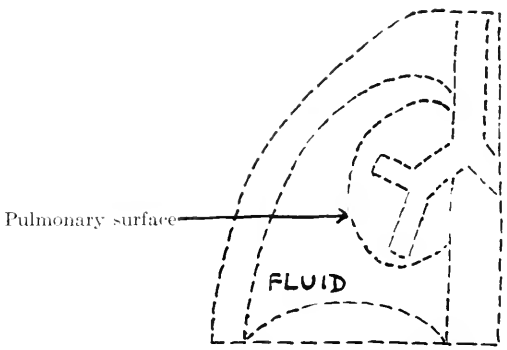

FIG. 4.—Pleural effusion. Lung solid. No special reflection, the entire distance between bronchial wall and outer chest surface. Compare solid lung. Special diffusion may exist between lung and chest wall. Vocal resonance may be increased. Bronchi in diagram represent small as well as large bronchi.

combination, offer any serious impediment to the passage of sounds. If, then, diffusion is limited, the conditions are very much as in the case of the solid lung unassociated with fluid. And whatever the degree of diffusion, due to separation of the lung from chest wall and other factors, the conditions are very much the same as though tissue replaced fluid in the pleural cavity. The explanation is entirely satisfactory where the solid lung is separated only a short distance from the chest wall by the fluid, but it is well known that very large effusions on either side of the chest separating the lung a great distance from the chest wall, and thereby greatly increasing the diffusion between lung and chest wall, may furnish striking examples of cases with increased vocal resonance. In such cases it seems likely that some vibrations are received at the periphery of the chest *coming straight across through the fluid from the trachea.* The physical conditions are certainly favorable for this,

that is, the fluid may be present in the upper part of the pleural cavity, so that in the course of the vibrations from the trachea to the chest wall no air intervenes, but only tissue and fluid. Very

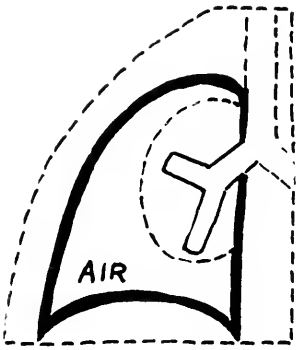

FIG. 5.—Pneumothorax. Lung air-bearing. Special reflection (indicated by heavy line) at air chest-wall junction. Reflection at outer bronchial surface as in Fig. 3. No special diffusion; diffusion being limited by the heavy walls enclosing the air in the pneumothorax cavity. Vocal resonance distinguished. Bronchi in diagram represent small as well as large bronchi.

loud sounds may be obtained over the chest of a fetal calf after fluid has been introduced between the chest wall and the solid fetal lung, these sounds becoming much weaker, however, after inflation of the lung. (The sound in this case is introduced into the trachea.)

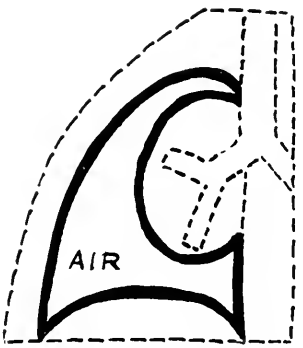

FIG. 6.—Pneumothorax. Lung solid. Same as Fig. 5, except that there is special reflection (indicated by heavy continuous line) between solid lung and surrounding air, while there is no reflection between outer surface of bronchi and surrounding solid tissue. Vocal resonance diminished. Bronchi in diagram represent small as well as large bronchi.

Pneumothorax. In the case of pneumothorax the distinctive location of sound loss is at *the junction of the air in the pneumothorax cavity with the chest wall*, where reflection of the vibrations

acts very powerfully as a result of the enormous differences in density of air and tissue. If the collapsed lung is air-bearing the opportunities are more favorable for the transmission of sounds to the periphery of the chest than if the lung is solid, because more sound can enter and leave a collapsed air-bearing lung under these conditions than when the lung is solid, while at the same time the air-bearing lung itself is a very good transmitter of sound. If no adhesions exist at the apex sound may be obtained coming directly from the trachea to the chest periphery by way of the pneumothorax cavity. *Diffusion exerts little effect between the lung and the chest wall*, the sound intensity being fairly equal throughout the pneumothorax chamber, because the air is enclosed within solid walls. The diminished vocal resonance is probably partly due to the small size of the collapsed lung and the consequent diminished calibre of its bronchi, resulting in the admission of a reduced amount of sound into the affected lung. When a patulous fistula exists between the pneumothorax cavity and a bronchus, the conditions are favorable for abnormally loud vocal resonance.[4]

[4] Some of the subjects briefly presented in this paper have been treated more fully in the Tenth Report of the Henry Phipps Institute for the Study, Treatment, and Prevention of Tuberculosis, in an article by Montgomery and Eckhardt, entitled "Pulmonary Acoustic Phenomena."

REVIEWS

DISEASES OF CHILDREN. By EDWIN E. GRAHAM, M.D., Professor of Diseases of Children, Jefferson Medical College, Philadelphia; Pediatrist to the Jefferson Hospital and to the Philadelphia Hospital; Consulting Pediatrist to the Training School for Feeble-minded, Vineland, N. J.; Member of the American Pediatric Society, etc. Pp. 902; with 89 engravings and 4 plates. Philadelphia and New York: Lea & Febiger, Publishers, 1916.

THIS work makes another addition to the rapidly growing number of complete text-books on Pediatrics. In general it conforms to the best orthodox forms of such publications brought "down to date." Apart from a general commendation of a book which the practising physician may accept as giving a reliable account of disease in childhood, certain features may be especially noted. The chapter devoted to infant mortality, heredity and environment is most timely and appropriate and should indicate to every thinking physician the importance of "preventive" as contrasted with "curative" medicine. Another chapter on the role played by fresh air in the treatment of disease should also be included in the same category as it forms a plea for the value of fresh air in health as well as in sickness. A special chapter on puberty discusses in a much more extensive manner than is usual a subject upon which the average physician has ideas scarcely less hazy than those of the laity. Another chapter of practical importance is that on dentition—that much overrated but not to be overlooked unit in the physiological development of the child. The relation of the teeth to disease also is adequately considered. Throughout the book treatment is indicated in a way which is most likely to benefit the general practitioner, with the proper warning against the much-to-be-deprecated overzealous medication. The subject of infant feeding admittedly is the most difficult one to present in the whole range of pediatrics, and it would seem to the reviewer that the author has not developed it in the most logical order. The information, for the most part, is there, but the difficulty of securing an adequate conception of the relation of food to digestion and the results of indigestion has not been solved as satisfactorily as the author's knowledge and experience would warrant. Another point for criticism is to be found in the failure to follow the modern tendency toward the simplification

rather than the multiplication of diagnostic titles, especially on the subject of the digestive disorders of infancy. A few omissions are to be noted, but on the whole the book covers the range of the diseases of childhood in a manner more than usually thorough.

J. C. G.

A Text-book of Human Physiology. By Albert P. Brubaker, A.M., M.D., Professor of Physiology and Medical Jurisprudence in the Jefferson Medical College. Fifth edition. Revised and Enlarged; with 1 colored plate and 359 illustrations. Philadelphia: P. Blakiston's Son & Co.

After paging through this new edition and comparing it with the previous edition one is impressed with the thoroughness of the revision. Changes are numerous but not violent. This indeed would have been a mistake for the preceding edition was not only pedagogically sound, but satisfactory as to the relative importance which was given to the data presented. The thoroughness rather manifests itself in the form of splendid conservatism in the selection of new material. In spite of the introduction of much new data the book is little enlarged, for many omissions of the proper sort have been made.

Changes of a minor character are seen in the first chapters on the chemical composition of the body, the physiology of the cell, of the skeleton, of the muscle tissue, and of the nerve tissue. Diagrams and illustrations have been modified, and sometimes replaced by others. Much more bold type is used, which make the volumes more efficient as a reference book. These changes distinctly improve these chapters which had already reached a high degree of excellence in the previous edition.

The chapter on food has undergone considerable change. The description of a modern metabolism experiment is concise and clear. The chapter on digestion shows considerable revision. The physiology of the sphincter cardiæ, and the movements of the intestines has been brought up to date. In the chapter on circulation a couple of pages are devoted to the electrocardiogram. Arterial pressure is also given more consideration. The physiology of the vasomotor mechanism also shows advantageous changes of treatment and some new material is added. Calorimetric measurements are considered in greater length in the chapter on respiration. Internal secretions have also received much attention, for changes of an important character are noted. If space permitted it could be shown that the other chapters have received painstaking attention as indicated by the changes of both a major and a minor character.

The book has been written by an author who knows the philosophy

of pedagogy and who is widely read in the various ramifications of the subject. He knows well how to weigh the relative importance of the material presented by researchers of the present day and to combine it with the older information in the proper proportion. E. L.

Diseases of the Digestive Tract and their Treatment. By A. Everett Austin, A.M., M.D., Assistant Professor of Clinical Medicine, in Charge of Dietetics and Gastro-intestinal Diseases, Tufts College. Pp. 552; 85 illustrations. St. Louis: C. V. Mosby Company, 1916.

This volume, the latest arrival in the rapidly growing number of monographs dealing with gastro-intestinal subjects, while not so good as some of its predecessors, nevertheless presents features which speak in its favor.

While by no means an exhaustive treatise of the subject, and not intended as such, it contains a great deal of practical information, derived from a clinical experience covering a quarter of a century, which should prove useful to both students and general practitioners, although it may not appeal so strongly to men who are specializing in this subject and who are familiar with the best books in this and other languages.

To the reviewer, who does not wish to be unduly critical, it would seem that the book is badly balanced in regard to the space allotted to different topics. For instance, one-half of the volume is taken up with a discussion of the anatomy and physiology of the gastro-intestinal tract; the examination of the patient, historical, symptomatic, and physical; the methods of applying laboratory aids in diagnosis; a chapter on dietetics, which is one of the best in the book; and a chapter on treatment in general, which is fairly well presented and forms a good working basis, though unfortunately is far from being up to date. These chapters make up Part I of the volume. Part II is devoted to a discussion of special gastric diseases which, in the opinion of the reviewer, are afforded scantier treatment than they deserve, only 66 pages being given to the organic diseases and 24 pages to the functional disturbances. In regard to the former only five conditions are presented, namely, gastritis, ulcer, ectasia, cancer, and splanchnoptosis, no mention being made of sarcoma, syphilis, tuberculosis, benign tumors of the stomach, benign pyloric stenosis, and congenital defects, topics which while of less importance than those discussed, nevertheless deserve a place in a treatise of this size. Again, in regard to functional disturbances no mention is made of some of our more recently acquired knowledge of vago- and sympatheticotony. Part III, consisting of 143 pages, is taken

up with a discussion of special intestinal diseases, and for the most part is much more creditably handled than is Part II. There is no space allotted to a discussion of diseases of the mouth, the esophagus, the pancreas, and the biliary apparatus in their direct or associated influences on gastro-intestinal digestion.

The author shows commendable familiarity with the foreign literature, especially from German sources, but has paid very little attention to the marked advances in and the many contributions to the subject which have recently been developed by American writers. For a book published as late as the current year it is almost unpardonable that no mention should be made of newer methods of diagnosis by fractional gastric analysés, gastric and duodenal sediment studies, and the development of some of the more recent biological and physiological chemical tests, useful in differential diagnosis. The book is presented in a literary style which is somewhat too refreshingly breezy in its use of slang expressions that seem out of place in such an otherwise dignified treatise, and the reviewer occasionally found himself lost in a maze of badly constructed sentences, for instance the following: "This peristaltic action of the antrum plays a very important part in the act of vomiting. At first the muscular tone of the fundus relaxes, leaving its walls flabby; the cardia opens and the waves of the antrum continue, but against a closed pylorus and a relaxed fundus, in which way the contents of the stomach, perhaps aided by the pressure of the diaphragm and the abdominal walls, with mouth open, posterior nares and glottis closed, as in swallowing, are forced out of the mouth."

From the publisher's stand-point the book is attractively bound and printed, and the somewhat mediocre illustrations have been capably reproduced. B. B. V. L.

Skin Cancer. By Henry H. Hazen, A.B., M.D., Professor of Dermatology in the Medical Department of Georgetown University; Professor of Dermatology in the Medical Department of Howard University; Some Time Assistant in Dermatology in the Johns Hopkins University; Member of the American Dermatology Association. Pp. 251; 98 illustrations. St. Louis: C. V. Mosby Company, 1916.

The attractive little book of Hazen's with the title of *Skin Cancer* has been read from cover to cover with great pleasure and interest by the reviewer. The subject under consideration has been divided into nineteen chapters: general considerations; precancerous dermatoses; epithelial warts; basal-celled carcinomata; cubo-celled carcinomata; spino-celled carcinomata; benign and

malignant tumors of the cutaneous appendages; multiple benign tumors; nevocarcinomata and malignant melanomata; carcinoma en cuirasse; endotheliomata; benign connective-tissue tumors; sarcomata and sarcoids; lymphomata; differential diagnosis; prognosis; prophylaxis; treatment; tumors according to location.

The volume is well illustrated and the various histopathological cuts emphasize clearly the various portions of the skin from which the growths may arise. The classification of these various growths has always been an extremely difficult matter and the writer has been extremely clear in his differentiation of the various types. Emphasis has rightly been given to the fact that the type of treatment should depend upon the character of the cells comprising the tumor and the portion of the skin from which they arise. The dictum is again broached that lesions which eventually may give rise to malignancy should be removed in their incipiency. The suggestion might be offered that the various sarcoids are probably of tubercular origin and therefore should be removed from a future edition.

The book is commended to all those interested in the scientific and also practical side of skin cancer. J. C. K.

ANLEITUNG FÜR DIE KRIEGSCHIRURGISCHE TÄTIGKEIT. Von Prof. Dr. LOTHAR DREHER, Leiter der Orthopäd; Abteilung und Oberärzt an der chirurgischen Universitätsklinic in Breslau. S. 158, mit 132 Abbildungen. Berlin: S. Karger, 1916.

THIS war brochure is divided into two parts. After an introduction the general part deals with the subjects of organization, variety of weapons, disinfection in the field, dressings, infection, general effects of gunshot injuries upon the body, narcosis, and local anesthesia. The special part covers gunshot wounds of the extremities, skull, face, neck, thorax, spine, abdomen, and urinary tract, and then concludes with frost-bites, appendicitis, suppurative lymphadenitis, furuncle, and carbuncle. Each subject is considered under two headings—first aid and later treatment.

There is no subject less desirable to commit between the covers of a bound book than that of the surgery of the present war, for revolutionary advances are daily being made, based upon the try-out of different methods by 100,000 surgeons on the various battle fronts, the discovery of new methods by investigators like Carrel and Dakin, and the constant sifting of data by collaborators to establish the best means of procedure. Thus in the book before us the sole treatment recommended for gas phlegmon is the radical and obsolete one of amputation. The prophylactic treatment of tetanus is not referred to, yet since the routine use of tetanus anti-

toxin for a year and a half there have been practically no cases of tetanus treated in France or England. Nitrogen-gas compression of the lung, a valuable procedure in selected cases of continuing hemothorax from lung injuries, is not mentioned. That sovereign remedy for shock—direct blood transfusion—is omitted from the therapeutics of shock, as is its efficient substitute, intravenous saline infusions with adrenalin. Heart massage in emergencies is not described. Trepanation by means of hammer and chisel, as recommended in the book, is a perfectly good way of increasing shock already present. Auscultation is a much gentler method than manipulation in the diagnosis of complete fracture of a rib.

The more one considers the matter the less reason one sees for the publication of these war manuals, from the practical stand-point at least, although they doubtless have their place in a course of study at a military medical school. The surgical teachings from previous wars are being daily controverted, as Fauntleroy has recently shown in reviewing the surgical lessons of the European war. The outstanding feature of all serious wounds in this war is the mutilating and devitalizing effect on the tissues due to large and small irregular pieces of metal, the majority of which are fragments of the high-explosive shell and hand grenade.

As previously pointed out in these columns, in the penetrating and perforating injuries of the abdomen the field surgical experiences of the South African war seemed to prove conclusively that opium, starvation, and rest in the Fowler position yielded better results than treatment by operation. It would seem, from reports, that the contrary is the case in the present war. Where it has been possible for the patient to receive prompt attention the results from operative treatment have been most encouraging in improving the statistics as compared with the expectant line of treatment. As Carrel has rightly stated: "The future of the wounded depends upon the rapidity of transportation and the possibility of treating the wounded as soon as possible."

We hope that we have succeeded in pointing out the uselessness of these manuals in the heat and turmoil of surgical work in the field. That they have a distinct placé as collateral reading for the first-aid instructions now being published in the daily press, will not, however, be gainsaid. P. G. S., Jr.

Hay Fever: Its Prevention and Cure. By W. C. Hollopeter, M.D., Attending Physician to St. Joseph's Hospital, etc. Pp. 292; 5 illustrations. New York and London: Funk & Wagnalls Company, 1916.

This treatise on hay fever is a rather conglomerate compilation of antique, medieval, and modern views on the etiology, pathology,

and treatment of hay fever, accompanied by a very complete bibliography covering the literature from 1565 to 1916. The opinions of various authors are quoted freely even to the insertion of extensive abstracts from leading articles. In spite of this elaborate consideration of the literature the author's own conception of the etiology and pathology of hay fever is, to say the least, most confusing. Also, his proposition that local treatment of the nasal mucosa and the nasopharynx with douching and swabbing will effect a cure in the large majority of cases seems a rather extravagant claim. As a book for reference this work will be found most useful, but as a text-book it is too confused and misleading. G. B. W.

THE DESCRIPTION OF AN OPHTHALMOSCOPE. A TRANSLATION OF VON HELMHOLTZ'S "BESCHREIBUNG EINES AUGENSPIEGELE." By THOMAS HALL SHASTID, A.B., A.M., M.D., LL.D., F.A.C.S. Chicago: Cleveland Press.

FEW medical instruments have served their purpose better or fulfilled the early predictions of their originators to a greater extent than the ophthalmoscope. When one pauses to consider the knowledge and facts that have been contributed to medical subjects through its use it is nothing short of remarkable that sixty-five years should elapse before there should appear a translation of von Helmholtz's original description. For his successful efforts in placing this historic and epoch-making contribution at the disposal of many who otherwise would have been deprived of the privilege of reviewing it, Shastid deserves the thanks of the English-speaking profession. The small volume contains but thirty-three pages, the subject being discussed under four headings; (1) illumination; (2) production of a distinct image of the retina; (3) description of the ophthalmoscope; (4) viewing the retina and the image of the flame. The frontispiece shows a reproduction of the original illustration in von Helmholtz's *Beschreibung eines Augenspiegels*. T. B. H.

HARVEY'S VIEWS ON THE USE OF THE CIRCULATION OF THE BLOOD. By JOHN G. CURTIS, M.D., LL.D., formerly Professor of Physiology, Columbia University, in the City of New York. Pp. 189; 4 illustrations. New York: Columbia University Press.

THE author bases his consideration on very thorough translations of Harvey's Latin treatises. Harvey's private lecture notes are also freely quoted, as well as several other Latin and some Greek writings. Harvey's references are traced to their source.

It will be recalled that in 1602, when Harvey received his doctor's degree at Padua, Galen and Aristotle were still undisputed authorities. It was against the accepted thories, and such other obstacles as weak magnifying glasses, that the "discoverer of the circulation" had to contend. Moreover, much that he could demonstrate he could not explain. Contrary to the other eminent men of his day, Harvey was not dazzled by the past, although he admired it. All these facts are clearly brought out in several chapters.

It is interesting to the present-day physiologist to find some of the theories held by Harvey on the cause of the heart beat. Thus: "I judge the cause of the diastole and expansion to be the innate heat and expansion to occur first in the blood itself, gradually thinned and swelling up like matters in fermentation." The book abounds with such delightful contrasts to modern teaching while showing with what clearness the mind of a great observer grasped the fundamentals of the problem of circulation. A. G. M.

Medical Lectures and Aphorisms. By Samuel Gee, M.D., Fellow of the Royal College of Physicians; Honorary Physician to H. R. H. the Prince of Wales, and Consulting Physician to St. Bartholomew's Hospital. With Recollections by J. Wickham Legg. Pp. 408. Henry Frowde, Oxford University Press; Hodder & Stoughton, Warwich Square, London, E. C.

This book has no new ideas to present. It is, however, very entertaining reading and contains a great many wise sayings. Dr. Gee was of the old school, well versed in the literature of the ancients, eminently observant, of an analytical mind, and at the same time opposed to experimentation as a method of studying nature. He on several occasions refused to give the Harveian oration because it imposed upon the orator the condition of finding out the ways of nature by experiment. Yet he has presented here a work not only of literary charm but of value because of its searching analysis of human nature, its therapeutic suggestions, and above all its presentation of certain medical problems from the purely practical point of view. T. G. M.

Wish Fulfilment and Symbolism in Fairy Tales. By Dr. Franz Ricklin, Zurich. Authorized translation by Dr. William A. White, of Washington, D. C. Pp. 90. New York: The Nervous and Mental Disease Pub. Co.

This is a very interesting Freudian interpretation of fairy tales. According to the author all fairy tales have as their object the

accomplishment of certain wished for results. There is always someone in the tale who will marry either a prince or a queen and according to the Freudian views the structure of these tales is analogous or stands in close relationship to dreams, hysteria or similar symbolic features found in some forms of mental disease. Of course, the author proves to the satisfaction of anyone who believes in Freudian psychology that the leading motive is the sexual. Those who do not believe in Freudian psychology will perhaps deem it a pity that perfectly good fairy tales should be analyzed and laid bare and given a sexual meaning. However, whether one believes in it or not the book is very interesting reading, and once begun the reader is bound to finish the volume.

T. H. W.

Injuries of the Eyes, Nose, Throat and Ears. By A. M. Ramsay, M.D., F.R.F.P.S., Ophthalmic Surgeon, Royal Infirmary, Glasgow; J. D. Grant, M.D., F.R.C.S., King George Hospital, London; H. L. Whale, M.D., F.R.C.S., Captain R.A.M.C. (T.F.), the County of London War Hospital, and C. E. West, F.R.C.S., Aural Surgeon to St. Bartholomew's Hospital. Pp. 160; 11 illustrations. London: Oxford University Press. Published by the Joint Committee of Henry Frowde and Hodder & Stoughton.

This book is a valuable pocket primer not only to the army field surgeon, but to all interested in first-aid work. It is based chiefly upon the experience gained at the front in the base hospitals of the present European war.

There are sixty-five pages devoted to the injuries of the eyes, the chapter on amblyopia due to traumatic neurosis being of special value to the neurologist. The treatment of wounds is presented in a practical manner, the methods mentioned being only those that were found to meet all requirements at the front.

It is to be regretted that more space is not given to injuries of the ear, at least in proportion to that given the other headings. The differential diagnosis between nerve deafness and that caused by an obstructive lesion is rather lightly dealt with. B. D. P.

The Stretcher Bearer. By Georges M. Deputy, M.D. Pp. 138. London: Oxford Medical Press.

The importance of first-aid stretcher drill has prompted the author to publish this collection of illustrations of the method of handling and carrying the wounded. It serves as an addition to the *Royal Army Medical Corps Training Book*. G. M. L.

Injuries to Joints. By Major Robert Jones, R.A.M.C. (T.). Pp. 189; 29 illustrations. London: Oxford Medical Press.

In this day of "preparedness," when practitioners are studying some of the chapters of military surgery, this volume by Robert Jones is highly to be commended. The earlier chapters, dealing with the general principles of injuries to joints, their symptoms and treatment are written in a style that is a model for surgical teaching. The reasoning is based on anatomy and pathology and is clear and logical. There follows a systematic review of the various joint injuries and fractures and a definite plan of treatment is given. The book is remarkably free from the vague statements usually found in treatises on joints. G. M. L.

Gunshot Wounds of Bones. By Captain Ernest W. Hey-Groves, R.A.M.C. (T.). Pp. 134; 34 illustrations. London: Oxford Medical Press.

Modern methods of treatment have been under trial sufficiently long for the author to present in text-book style those that have proved most applicable to gunshot injuries in military surgery. Necessity has led to the development of ingenious applications for the immobilization of fractures since the bone plate has failed and the bone graft can rarely be used on account of infection.

G. M. L.

Painless Childbirth Eutocia and Nitrous Oxide-oxygen Analgesia. By Carl Henry Davis, A.B., M.D., Associate in Obstetrics and Gynecology, Rush Medical College, in affiliation with the University of Chicago; Assistant Attending Obstetrician and Gynecologist to the Presbyterian Hospital, Chicago. Pp. 134. Chicago: Forbes & Co., 1916.

This interesting monograph is an authoritative statement of the value of nitrous oxide oxygen analgesia in labor. A short history of anesthetic agents and their use in labor is given and the relative merits and dangers of each are discussed. The technic of the administration of this particular form of analgesia is described in detail. The obstetrical results in a group of parturient women so treated are given and contrasted with the results in a group delivered under average normal conditions. It was found that labor was shortened 25 per cent., and that no harm resulted to mother or child from its use. Properly administered, the cost was comparatively slight and a safe and successful analgesia easily secured. The book will be of interest to all concerned with this problem of obstetrics. P. F. W.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
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The Epidemiology of Lobar Pneumonia.—Of all acute infectious diseases lobar pneumonia is responsible for the greatest number of deaths in the United States. Previous observations by Dochez and Avery strongly suggest that in most cases the infection is acquired by transmission of the infectious agent from a recovered case which still harbors in the mouth the organisms responsible for the disease. The present study undertaken by STILLMAN (*Jour. Exper. Med.*, 1916, xxiv, 651) was made to determine the following points: first, to study the varieties of pneumococci present in the cases of lobar pneumonia admitted to the Rockefeller Hospital during the past four years; second, a study of the different types of pneumococci present in the mouths of normal individuals; third, to determine how often the disease-producing types of pneumococci occur in the mouths of normal persons; fourth, to determine if possible the frequency of the occurrence of the disease-producing types in the mouth secretions of healthy people associated with cases of pneumonia and, finally, to determine the period of time during which convalescents harbor in their mouths the types of pneumococci which have been responsible for their disease. The results which can be briefly summarized, are in general a confirmation of the previous observations reported from the Rockefeller Institute. The commonest types of organisms responsible for lobar pneumonia are those of groups 1 and 2. The types of pneumococci most frequently found in the mouths of healthy people are those of groups 3 and 4, the latter especially. These organisms are responsible for the minority of cases of lobar pneumonia. Intimate association with cases of lobar pneumonia may lead to the harboring in the mouth secretions of healthy people of the highly parasitic pneumococci or groups 1 and 2. In

addition some evidence was secured to show that true carriers of groups 1 and 2 may be encountered in individuals who have been in no contact with an infected patient, so far as is known. There can be no doubt but what convalescents from lobar pneumonia may carry for long periods of time in their mouths the type of pneumococcus with which they were infected. These facts may throw much new light upon the epidemiology of this disease and subsequently bring to light very important factors concerned in the transmission of pneumonia from one individual to another.

The Influence of Age upon the Venous Blood-pressure in Man.—D. R. HOOKER (*Am. Jour. Physiol.*, 1916, xl, 43) has recorded observations on the venous blood-pressure in normal individuals at different ages. The author used the method he described in 1914 (*Ibid.*, xxxv, 73), the pressure being recorded in centimeters of water. The subjects were grouped in decades, and each figure represents the average of determinations on at least 50 individuals. Cardiac disease was excluded in the subjects studied. "Because of the uncertainties of illumination, the pressures were read at complete collapse of the vein and not, as is more accurate, at the point at which the shadow comes and goes with slight oscillations of the outside pressure." The values are therefore some-what high: 5 to 15 years, 8.30 cm.; 15 to 25 years, 12.66 cm.; 25 to 35 years, 15.00 cm.; 35 to 45 years, 17.98 cm.; 45 to 55 years, 19.04 cm.; 55 to 65 years, 24.17 cm.; 65 to 75 years, 25.59 cm.; 75 to 85 years, 26.00 cm.

The Effects of the Subcutaneous Injection of Organ Extracts upon the Flow of Pancreatic Secretion.—J. ROGERS, J. M. RAHE, G. G. FAWCETT AND G. S. HACKETT, (*Am. Jour. Physiol.*, 1916, xl, 12) report studies made on the dog on the effect of aqueous extracts of organs upon the flow of pancreatic secretion, which they summarize as follows: The effect of the subcutaneous injection in dogs of the residue, or non-coagulable portion, of an aqueous extract of the liver is the immediate and vigorous stimulation of the external secretion of the pancreas. The residues of the thyroid and thymus produce a somewhat less vigorous and later response. The residue of the pituitary and parathyroid glands and of the spleen and pancreas are inert. The residue of the adrenal gland, like adrenalin, vigorously inhibits the intestinal secretions of the pancreas. Only the residue or non-coagulable portion of an aqueous extract of the above mentioned organs shows any appreciable effect upon the intestinal secretion of the pancreas.

The Nature of the Active Principle of the Retroperitoneal Chromaffin Tissue.—M. E. FULK and J. J. R. MACLEOD (*Am. Jour. Physiol.*, 1916, xl, 21) refer to the theory that all chromaffin tissue, whether contained in the suprarenal gland or not, yields adrenin, or a substance having a similar pharmacodynamical action. Vincent has pointed out that this theory is based upon the provisional assumption that chromaffin tissues are specific in their nature and everywhere of the same essential character. In support of this hypothesis, Biedl and Weisel have shown that extracts of the retroperitoneal chromaffin tissues in man have the same effect on arterial pressure as extracts of the suprarenal glands. The authors have employed other pharmacodynamical

tests, namely, the action on the spontaneous contractions of the isolated intestinal muscle and on the tone and contractions of the virgin uterus of the rabbit. An inhibition of the former, along with an augmentation of the latter, was taken as positive evidence of the presence of epinephrin. Acid extracts of the retroperitoneal chromaffin tissue of man, the dog, the cat, the rabbit, the guinea-pig, the white rat, the calf, the sheep and the pig were found to have the same physiological action on intestinal and uterine muscle as the active principle of the medulla of the suprarenal glands.

The Movements of the Mitral Cusps in Relation to the Cardiac Cycle.—A. L. Dean, Jr. (*Am. Jour. Physiol*, 1916, xl, 206) has experimented on the cats heart to determine the exact time relation in the cardiac cycle of the closure of the mitral cusps. A human hair has been attached to one of the mitral cusps, the movements of which have been recorded photographically. He has found that the movements of the mitral cusps vary somewhat with the length of the As–Vs interval. When this averages 0.272 second or more, the cusps move ventricleward slighly a short period after the onset of auricular systole. Toward the end of auricular systole they move auricleward quickly and markedly, but not to a position of complete closure. At the onset of auricular diastole the cusps move quickly ventricleward, the rapidity depending upon the existing intra-auricular pressure. When ventricular tonus is low, and when this obtains, there is a rebound of the cusps from the ventricular walls. The valves remain open until ventricular systole begins. At the onset of ventricular systole the cusps immediately move upward to a condition of complete closure, and remain so until ventricular relaxation begins. During active relaxation of the ventricles the cusps move downward to a lower position than they occupied at the beginning of cystole. From this position they gradually float upward during diastasis. The sequence of movements above described also occurs when the As–Vs interval ranges from 0.147 to 0.272 second, except that time is lacking for a complete opening of the valves before ventricular systole again causes their closure. The valves open slightly during the intersystolic period, the extent increasing with the As–Vs interval. When the As–Vs interval is less than 0.147 second the valves are in the process of closing due to the auricular effect when ventricular systole begins. Hence this cardiac event merely completes the closure already initiated by the auricle. There is in this case only a single closure movement, beginning before ventricular systole—a single movement, due in part to auricular contraction and in part to ventricular contraction. It is commonly taught that the mitral cusps are approximated at the onset of ventricular systole. It has been shown in this work that some degree of approximation obtains when ventricular systole begins if the As–Vs interval falls within limits that may be considered normal (0.13 to 0.18 second). It has been further shown, however, that the extent of this approximation is directly related to the length of the As–Vs interval, so that when the As–Vs interval equals 0.272 the cusps are as widely separated as at the onset of auricular systole. It is of practical importance to recognize that in cases of delayed A–V conduction the valves may undergo two distinct movements of closure, the first near the end of auricular systole, the second at the beginning of ventricular systole.

SURGERY

UNDER THE CHARGE OF

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A Study of the Anatomy, Pathology, and Treatment of Uterine Prolapse, Rectocele and Cystocele.—Frank (*Surg., Gynec. and Obst.*, 1917, xxiv, 42) says that with very few exceptions, anterior and posterior colporrhaphy combined with either the Alexander operation or ventrofixaton are applicable to all cases of prolapse or cysto-rectocele and retroverson both during and after the childbearing period. The technic of these plastic operations can be learned as precisely as that of inguinal hernia, if the student is taught the regional anatomy. To obtain the proper dimensions of the reconstructed canal, however, requires considerable experience and proficiency in operating. The disadvantage of the technic, which is described at length, is the considerable time required. A rapid operator cannot complete currettage, amputation of the cervix, anterior and posterior colporrhaphy, ligation of the tubes, and ventrofixation in much less than ninety minutes. In some cases (though very rarely) it may prove advisable to perform the vaginal plastic and the abdominal fixation at separated sessions (two weeks' interval).

The Actual Cautery in the Treatment of Chronic Ulcer of the Stomach.—Scudder and Harvey (*Surg., Gynec. and Obst.*, 1916, xxiii, 718) investigated experimentally, on dogs, Balfour's method of treating certain chronic ulcers of the lesser curvature of the stomach by the application of the actual cautery followed by suture of the cauterized area. It appears that the suture of the cauterized margins of the stomach wall is attended by practically a normal reparative process similar to the reparative process following a simple incision with the knife. The method is applicable to a chronic ulcer seated upon the lesser curvature so far away from the pylorus as to make its removal by excision difficult. Such an ulcer may be cauterized from the center out, as suggested by Balfour, so that the loss of substance occasioned by the cauterization may be as large as $1\frac{1}{2}$ inches or more in diameter and the edges may be then approximated with the assurance of a proper healing of the wound. Ulcers seated on the posterior wall of the stomach which are safely approached by a gastrotomy incision may have their edges thoroughly cauterized and also the base thoroughly cauterized even when it is adherent to the pancreas, and be sutured with the assurance to the surgeon that the reparative process will proceed satisfactorily. Certain chronic ulcers adherent to the posterior parieties and pancreas do not lend themselves to easy and safe excision and suture. The cautery is sometimes applicable to this special group of cases. It will destroy any beginning cancer in the edges of the ulcer if the cauterization is thoroughly done. In order to close the stomach following a simple excision of a portion of

the stomach wall, a very large wound remains to be sutured. Following the use of the cautery no such large gaping wound exists, and the stomach is closed more readily than after a wide excision by the knife. With cauterization as with simple excision, the stomach should be carefully mobilized and the part to be operated on controlled, so that the portion actually cauterized is rendered accessible. The suture material employed in human cases in each instance has been No. 1 chromic catgut. It has not been found necessary to reinforce the sutured area by interrupted linen suture of the peritoneal surface in all cases. If it is possible to place these interrupted linen sutures it is wise to do so. Following any extensive plastic of the stomach, a gastro-enterostomy should be done (Mayo).

Hemostasis by Interposition of Muscle, Fat and Fascia in Parenchymatous Organs.—Risley (*Surg., Gynec. and Obst.*, 1917, xxiv, 85) carried out a series of 12 experiments on dogs to determine the value of the above tissues in stopping hemorrhage in such organs as the kidney and liver, when other forms of hemostasis are either impossible or undesirable. He found that the ideal hemostatic in wounds of parenchymatous organs is interposed muscle taken at the time of operation from the patient's own body. Such muscle in order to most effectively stimulate fibrin formation should be jaggedly cut with a knife and not crushed as with a scissors cut, nor should its hemostatic properties be extracted by its contact with salt solution. Fascia and fat act to a more limited degree as hemostatics; fascia more than fat, but both very much less than muscle. In the liver, however, both fascia and fat seem at times to be very efficient hemostatics. These tissues readily unite to the bleeding surface to which they are sewed, and form a smooth, solid scar. Microscopical examination of specimens removed at varying intervals after operation show, in the absence of sepsis, a beginning transformation of muscle into fibrous tissue, a partial absorption of fat and change into fibrous tissue, no changes in fascial transplants, in practically every case a firm blending of the interposed tissue with the cut surface of the parenchymatous tissue, the formation of new blood channells and no degenerative changes of any note. He concludes therefore, that muscle, fascia and fat can be safely interposed into these tissues and after acting as immediate hemostatics later undergo fibrous change and form a firm union with the parenchymatous tissue.

THERAPEUTICS

UNDER THE CHARGE OF

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Some Studies of Theocin.—Christian (*Arch. Int. Med.*, 1916, xviii, 606) says that a fairly complete study of a small group of patients with acute nephritis or chronic nephritis or cardiorenal disease indicates

that theocin in patients with slight or no edema has little or no therapeutic value, inasmuch as diuresis is not constantly produced, elimination of nitrogenous substances quite often is slightly if at all increased and renal function is frequently decreased after giving theocin. In cardiorenal cases with marked edema theocin is of therapeutic value, because it produces, especially in conjunction with digitalis, an active diuresis with increased sodium chloride elimination, which decreases edema, a troublesome feature in these cases. Inasmuch as there is evidence that following an active diuresis renal function is depressed, an intermittent usage of theocin seems preferable to a continuous usage in cardiorenal cases with edema.

The Relation of Diet to Beriberi and the Present State of Our Knowledge of the Vitamins.—Vedder (*Jour. Am. Med. Assn.*, 1916, lxvii, 1494) says that as there are many conditions under which it is difficult for certain people and institutions to procure a rich and varied diet it is better to give simple dietary rules for the prevention of deficiency diseases. The rules are as follows: In any institution where bread is the staple article of diet, it should be made from whole wheat flour. When rice is used in any quantity, the brown under-milled, or so-called hygienic rice, should be furnished. Beans, peas, or other legumes, known to prevent beriberi, should be served at least once a week. Canned peas or beans should not be used. Some fresh vegetable or fruit should be issued at least once a week and preferably at least twice a week. Barley, a known preventive of beriberi, should be used in all soups. If cornmeal is the staple of diet, it should be yellow meal or water-ground meal, that is, made from the whole grain. White potatoes and fresh meat, known preventives of beriberi and scurvy, should be served at least once a week, and preferably once daily. The too exclusive use of canned goods must be carefully avoided. Vedder is sure that the strict application of these rules will eradicate scurvy and beriberi, and he believes that they would be equally efficacious in eradicating pellagra from the United States.

Studies in Prophylactic Immunization with Bacillus Typhi-exanthematici.—Plotz, Olitssky and Baehr (*Jour. Am. Med. Assn.*, 1916, lxvii, 1597) write concerning their experience with prophylactic immunization against typhus fever. The vaccine consisted of a suspension of fifteen strains of B. typhi-exanthematici in physiologic sodium chlorid solution which had been subjected to a temperature of from 58° C. to 60° C., for from half an hour to one hour. After being tested aërobically and anaërobically as to its sterility, the vaccine was then diluted so that each cubic centimeter contained about two billion bacteria, and 0.5 per cent. phenol (carbolic acid) or tricresol added. Three injections consisting of 0.5, 1, and 1 c.c., respectively, were given in five- or six-day intervals. In all, 8420 persons, members of 109 hospital, sanitation and other units in Serbia, Bulgaria, and Volhynia, were vaccinated against typhus fever during the epidemic of 1915–1916, an attempt being made to include in this number only the persons who were most exposed to the danger of infection. Of this number six developed the disease during the four months of the epidemic. Their experiences in the Balkans and Volhynia during the winter and spring of 1915–

1916 with the vaccine made of B. typhi-exanthematici would seem, therefore, to indicate that it is capable of reducing the incidence of the disease, although it does not produce an absolute immunity to typhus fever.

The Comparative Resistance of Bacteria and Human Tissues to Certain Germicidal Substances.—Lambert (*Jour. Am. Med. Assn.*, 1916, lxvii, 1300) says that it is recognized that an ideal germicide for use on infected tissues of the body is one that will kill the pathogenic microörganisms present without at the same time injuring the tissues. Lambert found that cells are more easily destroyed than bacteria by all but one (iodin) of the agents used. However, in the case of several, mercuric chlorid, sodium hypochlorite (Dakin's solution), potassomercuric iodid, argyrol and phenol—the difference is not great. It is interesting that no harmful effect whatever was seen from exposure of cells for one hour to 10 per cent. alcohol. The low bactericidal power of hydrogen peroxid, so popular among the laity, is noteworthy. It is possible, however, that on account of the fibrin-dissolving property of iodin, causing conceivably an inhibition of wound healing, some other substance may be found approaching more closely the ideal tissue disinfectant.

Alpha-iodin, Active Constituent in Thyroid.—Kendall (*Boston Med. and Surg. Jour.*, 1916, elxxv, 557) reports his investigations which seem to indicate that the active constituent of the thyroid gland is contained in alpha-iodin, a crystalline compound. There appears to be no other substance in the thyroid secretion which acts directly. This substance, given even in very small amounts, will supplant thyroid activity, relieving the conditions of myxedema and cretinism, and in excess will produce symptoms simulating exophthalmic goitre. It appears to have no direct action on the pulse rate. The extent to which the rate is affected depends not on the administration of the thyroid, but on the simultaneous ingestion of food, and in particular of amino-acids. This effect may be outlined as follows: After the administration of the compound, there is no apparent effect for many hours. There is no increased pulse rate, nor drop in blood pressure. However, if the thyroid hormone and amino-acids are injected simultaneously, the pulse rate is enormously affected, and even death may result, due to the apparently great increase in metabolism going on in the animal. It appears very probable that the thyroid hormone manifests its activity by reacting in some way with amino-acids.

The Toxicity of the Present Supply of Salvarsan and Neosalvarsan.—Ormsby, Mitchell, Moody and Ellis (*Jour. Am. Med. Assn.*, 1916, lxvii, 1756) all report a striking increase in the number of severe reactions following the injection of salvarsan and neosalvarsan recently imported from Germany. The toxic symptoms following salvarsan were strikingly vasomotor and accompanied or followed the injections. Marked generalized erythema, and in some cases urticarial wheals, appeared. Lacrimation occurred, followed by injection of the conjunctival vessels. The patient tossed the head from side to side in evident

respiratory embarrassment, and complained of a feeling of constriction about the chest. The pulse, at first full, quickly became rapid and weak, accompanied usually by pallor. In a few cases, nausea and vomiting occurred. The reaction following the injection of the present neosalvarsan differs from that of salvarsan in that there is a marked tendency to nausea and vomiting. In a few cases urticarial wheals have followed each injection, but the diffuse erythema, lacrimation and respiratory difficulty with fall of blood-pressure, observed after salvarsan, have not occurred.

The Administration of Arsenobenzol by Mouth.—Schamberg, Kolmer and Raiziss (*Jour. Am. Med. Assn.*, 1916, lxvii, 1919) say that experiments on animals have demonstrated that arsenobenzol (salvarsan) can be administered by mouth in solution as in capsules and become absorbed into the blood. The proof that absorption takes place is evidenced by the fact that a distinct destructive influence on trypanosomes in the blood of experimentally infected animals is exerted. Experimental studies on animals also demonstrated that arsenobenzol can be administered in capsule form over long periods of time without harmful results. Clinically they report that, during the course of four months, arsenobenzol in capsule form has been administered by them to about thirty patients in various stages of syphilis. The drug was given at first in ordinary gelatin capsules, but later in luterie capsules, in order to prevent the capsules being absorbed in the stomach. In a general way they found that the effect of the drug on the secondary eruption is much slower than after intravenous injection. Ordinarily it required about three weeks to cause the disappearance of a macular or papular eruption with the doses administered. In 1 case, however, a large papular syphilid of the face disappeared in three or four days, with almost the degree of rapidity that it would after an infusion of the drug into the blood. Tertiary nodular lesions required from two to three weeks' administration to affect their disappearance. In order to prevent oxidation of the arsenobenzol in the capsule, sodium hydrosulphite was incorporated with it, and a small amount of bismuth subgallate was added to prevent diarrhea. A capsule containing one-half grain of arsenobenzol was given after each meal, and in most patients no gastric or intestinal distress resulted. Some patients were able to take the capsules for six weeks without any distress. The authors do not advocate the use of salvarsan by mouth as a substitute for intravenous or intramuscular administration. It is not always possible, however, to administer salvarsan by intravenous or intramuscular injection. Inaccessibility of veins by excessive adiposity, thrombosis of veins due to repeated injections, or similar reasons may prevent intravenous injections. Another indication for the use of salvarsan capsules is as a supplementary treatment to intravenous administration. The disadvantage of intravenous salvarsan therapy is the fact that most of the drug is eliminated in a short time, but by combining the oral administration of salvarsan with the intravenous, a continuous source of the drug may be supplied to the blood. If it becomes necessary to administer a drug by mouth for the treatment of syphilis—the authors advocate salvarsan in preference to mercury, first, because it is a more powerful spirocheticide, and second, because it has a more

tonic influence than mercury. The cost of the drug might readily be a deterrent factor in prescribing salvarsan by mouth, as much larger doses are required to produce the same effect, in comparison with more efficient routes of administration. This method of treatment is to be reserved for special conditions and for particular cases.

OBSTETRICS

UNDER THE CHARGE OF

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Pregnancy Complicated by Parovarian Cyst. — Ahlström (*Jour. Svenska Läkaresallskapets Handlingar, Stockholm*, No. 3, 1916) reports the case of a pregnant woman at seven months who had a parovarian tumor which became twisted and incarcerated. The tumor had been pushed into Douglas's pouch by the pregnant uterus, and it is thought that the passage of hard fecal lumps through the rectum had resulted in twisting the tumor on its pedicle.

The Part Played by the Thymus Gland in Sudden Death in Newborn Infants. — Hammar (*Jour. Svenska Läkaresallskapets Handlingar, Stockholm*, No. 3, 1916) publishes the results of his study of microscopic sections of the thymus taken from sixteen children, some of whom are in the first days of life. Hammar, two years ago, published the results of his examination of the thymus in 14 cases of sudden death from various causes. The results of his studies lead him to believe that sudden death in the newborn does not result from active swelling of the thymus or any other condition of this gland. The thymus is often large in the newborn, but there is no evidence that this influences the vital state of the infant.

Malignant Chorio-epithelioma. — Engström (*Finska Läkaresallskapets Handlingar*, No. 8, 1916) previously reported 5 cases of malignant chorio-epithelioma of the uterus. He adds to this the results of minute study in a sixth case. In this patient the uterus and adnexa and part of the pelvic cellular tissue were removed. Metastases followed in the pelvis, liver, and left lung, from which the patient died. In this case four years had passed since the previous pregnancy which was the patient's fifth. The question naturally arises whether it is possible for fetal cells to remain latent in the uterus for four years before developing. Cases reported in the literature would indicate that this is possible. In one an interval of nine years had elapsed between pregnancies. So far as the best reported cases are concerned, it cannot be proved that this condition can remain latent so long, and the most natural explanation is found in the fact that a patient may be pregnant without suspecting it, the pregnancy terminating in a very early abortion.

Sterilization by Cautery Stricture at the Intra-uterine Tubal Openings.—Dickinson (*Surg., Gynec. and Obst.*, August, 1916) describes a method which he had devised and employed for sterilization which avoids direct surgical interference. It must first be ascertained that the patient is free from any condition which requires hysterectomy. The time chosen is from seven to ten days after a period. With the patient upon the back and the Sims speculum in place, the anterior lip of the cervix is seized by tenaculum forceps and held steady. From 5 to 10 minims of a 10 per cent. solution of novocain in adrenalin solution are then injected into the uterus and held there under pressure for a few seconds. Ten minutes are allowed for the anesthetic effect. The uterine canal is then wiped with Churchill's tincture or pure carbolic acid. The ordinary uterine sound, thoroughly sterilized, is then introduced and passed to the fundus and turned sidewise to find the cornu, and the exact distance of the cornu is noted. The cautery sound is then bent to fit the uterine sound, and has its slide pushed up so that the portion of the sound remaining exposed exactly equals the measurements of the uterine cavity already made by the sound. The cautery sound has a platinum point which can be heated by an electric current. When this is turned on the sound is applied against the cervix in plain sight, and the time is noted required to burn into the tissues enough to bury the platinum wire. The current is then turned off, the sound allowed to cool, and passed into the uterus to the cornu, then the current is turned on and the tissues at the cornu are cauterized by the heated platinum wire. Very little discomfort usually follows this application and the same procedure is carried out on the opposite cornu. On the cervix a slough forms which separates, leaving a clean granulating wound and this serves as an index of what is going on within. About three or four months after this procedure the patient may be examined by the roentgen-ray and a positive diagnosis made of closure of the tube by scar tissue. The writer describes similar procedures in other portions of the body where cauterization has been useful, and reasons by analogy that it will bring about the desired result where sterility is the object in view.

Hemolytic Anemia in Pregnancy.—In the *Ztschr. f. Geburtsh. und Gynäk.*, 1916, lxxi, No. 1, Esch contributes an extensive paper upon this subject. In all he reports 6 cases, 3 of whom died. In three of the patients there was hemorrhage in the retina, and in three the spleen was enlarged. This disease differs essentially from true pernicious anemia although when the blood is examined the results resemble those obtained in pernicious anemia. This develops in the second half of pregnancy, and is essentially a destructive process in the blood. Probably the resisting power normally present in the red corpuscles is greatly reduced or there is a great exaggeration in the natural physiological processes of hemolysis. Owing to the anemia these patients lack oxygen greatly and are partly anesthetized with carbon dioxid as a result. When in labor these patients seem to suffer much less than others. When they begin to improve their progress is rapid and there is usually no return of the anemia. In most cases pregnancy terminates prematurely in spontaneous labor and these patients do not improve until after delivery. The prompt termination of labor is usually the

best treatment and most of the children are lost as they have little power of resistance. Arsenic is the best remedy for this form of anemia. In 5 cases intramuscular injections of blood were given. Two patients seemed much improved after several injections; one had eight in all, 440 c.c. of defibrinated blood, the hemoglobin increase from 9 to 22 per cent. with corresponding improvement in other ways.

Pressure on the Brain as a Cause of Eclampsia.—ZANGEMEISTER (*Ztschr. f. Geburtsh. und Gynäk.*, 1916, lxxi, No. 1) believes that the clinical picture in cases of eclampsia points conclusively to pressure on the brain as the principle cause of convulsions; that treatment most successful in preventing and controlling eclampsia reduces the edema and irritation of the brain. When the uterus contracts the blood-pressure rises and adds to the pressure on the brain, and convulsions occur; on the contrary the blood directly relieves the condition.

Is the Operation of Cesarean Section Indicated in Breech Presentation?—MCPHERSON (*Am. Jour. Obst.*, November, 1916) has examined the records of 3412 cases of breech presentation and delivery among 97,000 confinements. An effort was made to ascertain accurately the cause of fetal mortality in these cases and to exclude all conditions which were not the abnormal presentation alone. As to the frequency of breech presentation, it is approximately 3 per cent. The mortality for the mother is practically that of uncomplicated spontaneous delivery when the head presents. In the series of cases studied the maternal mortality was 0.96 per cent. and was produced by placenta previa, chronic nephritis, chronic endocarditis, pneumonia, and other serious conditions. If these be excluded the mortality from the abnormal presentation only was 0.47 per cent. When the interests of the child are considered the death rate is about 10 per cent., and the difference in mortality between the children of primiparæ and multiparæ was practical nothing. McPherson criticises a recent paper whose author urges Cesarean section for breach presentation in primiparæ. When the cases reported were analyzed one had a submucous fibroid which would have prevented delivery through the vagina had the head presented. In the other case the pelvis was slightly contracted and it was thought that operation was safest for mother and child. While Cesarean section is not indicated for breech presentation only, it may be the safest method of delivery in some breech cases. In primiparæ at beyond the average age of childbirth and in whom the normal mechanism of labor does not develop the risk to the child in delivery in breech presentation is considerable, while the mother must sustain severe lacerations. If the child be large and well developed, in the interests of mother and child section is the safest procedure. So in justominor and rachitic pelves where breech presentation is present delivery by section is safest for mother and child.

Pregnancy Complicated by Pelvic Infection and Septicemia.—MOORE (*Am. Jour. Obst.*, November, 1916) reports the case of a rachitic negress who had a contracted pelvis and was delivered by Cesarean section. Three weeks after operation she developed multiple neuritis from which she finally recovered. In her second pregnancy she came

into the hospital and was delivered of a premature fetus. Two hours after delivery she had a severe chill followed by high fever and this was repeated on the following day. An examination of the blood showed a pure growth of Staphylococcus aureus. The patient made finally a complete recovery.

GYNECOLOGY

UNDER THE CHARGE OF

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Polycystic Kidney.—The results of the clinical experience with this condition at the Mayo Clinic are given in a recent paper by BRAASCH (*Surg., Gynec. and Obst.*, 1916, xxiii, 697). The series comprises 41 patients in whom at operation polycystic kidneys were found, although in only 26 of these had the condition been previously diagnosed. The average age of the patients was forty-six years, but 10 of them were under forty years and 7 were over sixty years. No material difference was noted with regard to sex. The predominant symptoms were pain, hematuria, tumor, and diminished renal function. The pain is not severe, as a rule, unless interference with urinary drainage or wide-spread infection occurs. There may be occasionally a dull pain in either loin, probably due to tension of the cysts. Hematuria occurred in 40 per cent. of the cases. It is evidently caused by the rupture of small bloodvessels in the cysts, and becomes manifest only when one of the cysts ruptures into the renal pelvis. It is usually stopped by puncture of the blood-distended cysts. Tumor was noted in 31 of the 41 patients, but was not always recognized as kidney, being occasionally mistaken for the liver or the gall-bladder. In only about half the cases was a bilateral tumor noted, in spite of the usual bilateral occurrence of the condition. The kidney function was directly estimated by the phthalein test in only 11 cases, being low in nearly all, and showing merely a trace of elimination in 2, both of whom died after operation. A normal phthalein and a normal specific gravity of the urine may be present, however, with polycystic disease, and such findings by no means exclude this condition. The chief value of the phthalein test is in differential estimation of the two kidneys, a point of great importance in determining upon the advisability of operation. *Treatment:* In 14 cases nephrectomy was done, a surprisingly high number in view of the fact that the condition is nearly always bilateral. The indications were large tumor with complete degeneration of one kidney (4 cases), unilateral lithiasis (3), diffuse infection (3), hematuria (2), traumatic rupture (1), and hydronephrosis (1). There was 1 postoperative and 1 subsequent death; 10 of the remaining patients were traced and found well after periods of one to ten years. The Rovsing operation (multiple puncture of the cysts) was done in 10 patients, with 2 postoperative and 1 subsequent death, the remaining

7 patients being alive at varying periods up to five years. The other case had merely exploratory operations, or the kidney condition was found incident to some other operation. The conclusions drawn by Braasch are briefly as follows: When there is marked clinical evidence of toxemia; when the blood-pressure is increased to 200 or more; when the various functional tests show marked renal disturbance, any operation is attended with considerable danger, and is of questionable value. When, however, there is evidence of but a moderate degree of renal insufficiency the Rovsing operation is followed by considerable benefit. Nephrectomy is indicated only in the presence of widespread infection, persistent hematuria, or destruction of renal tissue from mechanical obstruction, lithiasis, or other complication. It is, of course, possible only after the function of the remaining kidney has been demonstrated to be satisfactory, but under these conditions may be of great benefit.

Radium Treatment of Cancer of the Cervix.—A very brief report upon 9 cases of cervical carcinoma treated with radium at the Clarkson Hospital, Omaha, has recently been published by FINDLEY (*Am. Jour. Surg.*, 1916, xxx, 337). In 5 of these cases a radical hysterectomy was performed, followed, and in some instances preceded also, by the use of radium; in the remaining 4 radium was used without operation. In 3 cases, which were considered inoperable, the condition became frankly operable after the application of the curet, cautery, and radium. In 1 case scrapings from the cervix were of a highly malignant type, but careful search in the removed uterus showed only a nest or two of degenerated epithelium. One case was not favorably influenced by the radium, a recurrence in the vaginal vault manifesting itself shortly after three applications. In 2 cases pain was promptly relieved, in 4 it was only partly or not at all relieved, and in 1 it was apparently intensified by the radium treatment. One patient in whom the radium was used postoperative, developed a vesicovaginal fistula, which, however, promptly healed spontaneously. In one the general peritoneal cavity was invaded by cancer with such rapidity following hysterectomy and radium application as to suggest that the radium might have had a stimulating effect upon the cancerous growth. In 2 cases the patients failed to react well to the radium treatments developing a toxic condition, and it seemed possible that death was hastened by the action of the radium. Only two of the nine patients are still living, after periods of ten and fourteen months. In one there is no evidence as yet of recurrence, while in the other enlarged lymph nodes have lately developed in the right iliac region, and are strongly suggestive of recurrence. While the record here outlined certainly cannot be considered a very brilliant one, Findley thinks it fair to conclude that radium has a place in the treatment of cancer of the cervix, since it probably prolongs life in nearly all instances, and converts many inoperable cases into operable ones. The radium was applied in the cases discussed above in doses of from 32 to 62 mg., in properly screened tubes in the vagina, this being often supplemented by 20 mg. on flat applicators placed on the abdomen for the purpose of cross fire.

OTOLOGY

UNDER THE CHARGE OF

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A Case of Herpes Zoster Oticus.—By CAPTAIN ARCHER RYLAND (*Jour. Laryngol., Rhinol., and Otol.*, vol. xxxi, No. 12).—The patient, a man, was admitted to the Cambridge Hospital, at Aldershot, with the following symptoms: Pain in the depth of the left ear, aching pain and swelling of the left ear itself, slight impairment of hearing, but no discharge from the middle ear, weakness of the left side of the face, sensation of soreness on the left side of the throat and pain on swallowing, lachrymation of the left eye, dizziness with perception of rotation of objects from left to right. These symptoms, which followed each other in rapid succession, appeared in the following order: pain on the left side of the throat, pain and throbbing in the depth of the ear, burning pain, edematous swelling and livid discoloration of the auricle, followed by the appearance of herpetic vesicles on the floor and posterior wall of the left cartilaginous meatus, subsequent appearance of similar vesicles over the upper portion of the sternomastoid muscle and, later, left facial paralysis with vertigo and nausea. The facial paralysis occurred twenty-four hours after the vesicular eruption; throughout the illness the pulse was slow and the temperature subnormal, and dizziness and nausea were pronounced symptoms. On examination the left drum-head was found to be intact. There was some injection of the manubrial plexus and, in a lesser degree, of adjacent portions of the membranæ vibrans. There was no sign of increased tympanic pressure and there was an impaired audition for the lower fork tones and for the upper tone limit on the tone scale. The whole of the auricle was red and swollen with diminished cutaneous sensibility, and that part of the herpetic eruption which included the external ear was confined to the floor and posterior wall of the soft external meatus and of the conchæ. Discreet herpetic vesicles were present in addition on the skin overlying the mastoid process, with a similar slightly marked eruption distributed over the upper fourth of the sternomastoid and a few vesicles on the anterior surface of the left posterior faucial pillar. The anterior third of the left half of the tongue showed a few non-vesicular red spots, and there was some tenderness over the included area. These symptoms indicated implication of the following cranial nerves: Seventh, left facial paralysis not quite complete as regarded the orbicularis palpebrarum. Eighth, impaired audition but, at the time of admission, no signs referable to the vestibular ganglion. Ninth, disturbance of common sensation of the anterior third of the left half of the tongue, but no disturbance of taste. There was no spontaneous nystagmus, abnormality of pupils or of ocular movements of affection of the larynx. Six days after admission the auricle had recovered and its cutaneous sensibility had become normal,

the herpetic eruption was rapidly clearing, but remained most persistent on the meatus, the spontaneous nystagmus was still faintly present, the vomiting was less frequent, there was still some dizziness, the facial paralysis remained unchanged, and the leukocytes count was 8000 and the spinal fluid healthy. One month from the onset of the attack the facial paralysis was slowly recovering, there was a moist eczematous area corresponding to the region of the herpetic eruption, and some remaining impairment of hearing of the middle-ear type. The emphatic points in this case are, its suggestion in the first few days of the disease of an acute intracranial complication and the determination of the diagnosis by the early appearance of the herpetic eruption, which lasted for eight days following an auriculotemporal distribution, during the major portion of which from the beginning there was, in addition to the nausea, intense, frequent and uncontrollable vomiting, suggesting ganglionic involvement of the vagus; the spontaneous nystagmus made its appearance on the third day and its total duration was twelve days.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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The Etiology of Acute Epidemic Poliomyelitis.—MATHERS (*Jour. Infec. Dis.*, 1917, xx, 111) examined bacteriologically fresh material from 10 cases of acute poliomyelitis and isolated a peculiar polymorphic streptococcus-like organism in nine instances, in seven of which the growth has been pure. Similar organisms have been demonstrated microscopically in the tissues of the central nervous system of these cases. Cultures of this coccus injected into rabbits have produced paralysis of various groups of muscles, and characteristic lesions in the central nervous system consisting of hyperemia and edema of the tissues, with hemorrhages, round-cell perivascular infiltration, and neurophagocytosis in the spinal cord, especially in the gray substance, similar in every detail to the changes considered characteristic of acute poliomyelitis in man. This micrococcus has been recovered from the lesions in the inoculated rabbits by both cultural and microscopic methods. The artificial cultivation of the poliomyelitis coccus in an ascites-fluid tissue medium under anaërobic conditions causes changes in the media which cannot be differentiated from those previously described for cultures of the so-called virus of poliomyelitis. Morphologically, also, this bacterium when grown on the same media is

similar to the virus, and in stained smears it appears in minute Gram-positive coccus-like bodies arranged in pairs, groups and chains. These minute forms disappear when the organism is cultivated in other media under aërobic conditions. The morphologic, cultural, and pathogenic characters of the poliomyelitis coccus thus far determined indicate that it is an important factor in the disease.

Studies on Immunity in Typhus Exanthematicus with Reference to the Antibodies in Man and Guinea-Pig Demonstrable by the Dale Method.—Donzer and Olitsky (*Jour. Infec. Dis.*, 1917, xx, 99) state that antibodies against Bacillus typhi-exanthematici, demonstrated by the Dale method, are found in the serum of typhus-fever patients after the crisis. These antibodies are not present in the serum during the height of the disease. Antibodies against Bacillus typhi-exanthematici are found in the cells of typhus-fever guinea-pigs after the crisis. These antibodies are not demonstrable during the height of the disease. The reaction in the serum of typhus-fever patients and in the cells of the guinea-pig is specific; that is, by the use of similar methods no antibodies to Bacillus typhi-exanthematici could be demonstrated in the blood of normal individuals or of patients suffering from other infections. Guinea-pigs in the postcritical stage of typhus fever showed antibodies only to Bacillus typhi-exanthematici, and not to Micrococcus anureus, Bacillus typhosus, or Bacillus acne. The results with the Dale method offer further evidence of the etiologic relationship between Bacillus typhi-exanthematici and typhus exanthematicus.

Comparison of Methods for Disinfecting Swimming Pools.—Manheimer (*Jour. Infect. Dis.*, 1917, xx, 1) states that the value of ultra violet light as a disinfectant in swimming pools has not yet been definitely determined. Swimming pools equipped with ultra-violet-light apparatus showed lower bacterial pollution during its use, than before its use. A somewhat longer exposure of the water to the light would seem desirable; in most instances bacterial reduction was not observed after the water had passed through the ultra-violet-light apparatus. In regard to the method of adding chemicals to the water, it appears that the value of slow continuous addition or of single daily dosing varies with the chemical used. Copper sulfate gave better results when added gradually and continuously, while sodium hypochlorite gave the better results with single daily dosing. The relative efficiency of chemicals for water disinfection may be expressed as follows: (*a*) Calcium hypochlorite—high efficiency, low cost, not much care necessary in handling; (*b*) chlorin gas—efficiency high, cost very low, easily handled; (*c*) "lectrocide"—cost ten times as much as for hypochlorite, high efficiency, very easily handled; (*d*) copper sulfate—cost high, efficiency low, stains tiles, causes reduction in transpareney of water, easily handled. Final decision on a standard method for pool disinfection has not yet been reached, and cannot be until after ozone and other methods still under investigation have been fully tested. In the nine pools examined, refiltration was practised in all cases, a procedure which should be standard in all indoor pools.

Botulism.—Dickson (*Proc. Soc. Exp. Biol. and Med.*, 1916, xiv, No. 2) points out that the Bacillus botulinus may form its toxin in vegetable protein as well as animal protein. Experiments show that this toxin will develop when the bacillus is grown in beans, peas, corn, and apricots. The importance of these observations has been emphasized by the fact that within a few months there have been three outbreaks of botulism with eight deaths in which the cause of the poisoning was the ingestion of home-canned beans, corn and apricots, respectively. In all cases a number of chickens became paralyzed and died after eating the remnants of the food which had been discarded. The virulence of the toxin was very great in all cases, that in the beans and corn being so great that the patients died after merely tasting the contents of jars in which the odor was unusual. From the contents of the crops and gizzards of the chickens which died after eating the beans and corn, an organism was recovered which is morphologically and culturally identical with the Bacillus botulinus, and which produces a toxin by which the typical symptoms and the characteristic thrombosis may be reproduced in animals. The virulence of the toxin in both strains is extremely high, approximately 0.0002 c.c. of a filtered beef infusion culture of the bean strain being sufficient to kill a small guinea-pig within eighteen hours, and 0.001 c.c. of a similar culture of the corn strain being sufficient to kill a medium sized rabbit within twenty hours.

The Relation of Sewage Disposal to the Spread of Pellagra.—Siler, Garrison and MacNeal (*Proc.. Soc. Exp. Biol. and Med.*, 1916, xiv, No. 2) after a study of Spartan Mills in the city of Spartanburg, S. C., an endemic center of pellagra conspicuous for the number of cases of the disease which had originated in it, the surface privies were replaced by a water-carriage system of sewage disposal in the latter part of 1913 and the first half of 1914. Subsequent to this change there has been observed a remarkable reduction in the incidence of pellagra in this community, such that during the pellagra season of 1916 only one new case has appeared among the, approximately, 2000 residents upon the mill property and this one case originated in a house situated at the very margin of this sewered district and across the street from an unsewered house in which an old case of pellagra resided. Houses situated in the partly unsewered district adjacent to the mill property furnished several new cases of pellagra in 1916. The results of the experiment so far would seem to indicate that the improvement in sanitation has served to prevent the non-pellagrous population from contracting the disease, but has had relatively little influence upon the course of the disease in those who had previously contracted it. This result is quite in accord with the hypothesis announced by the Thompson-McFadden Pellagra Commission in 1913, in order to test which this experiment was undertaken.

Digestibility of Very Young Veal.—Langworthy and Holmes (*Jour. Agricul. Research*, 1916, vi, No. 16) state that throughout the United States little was known until recently regarding very young veal, since the sale of calves less than three to six weeks old for food is prohibited by Federal and State laws. Our attitude toward veal, as toward many other foods, has been determined in part by custom and prejudice

and in part by economic conditions and experience, often being illogical; therefore it is of interest to ascertain in such cases how far belief is justified by facts as shown by controlled experimental tests. That the common opinion that veal is less wholesome than beef and young veal less so than mature veal is not a consistent prejudice against young flesh foods is shown by the common and apparently growing taste which prefers squab to pigeon, ranks broilers as superior to fowls, considers sucking pig a great delicacy, and regards hot-house lamb—that is, lamb less than three months old and rapidly grown and fattened—as much superior to older lamb as lamb is to mutton. As determined by the experiments herein reported, the digestibility of the protein of bob veal is the same as that found for market veal—namely, 93 per cent., in round numbers. The subjects of both dietary and digestion experiments, so far as could be learned, experienced no physiological disturbances during the experimental period or afterward. The tests showed that such veal can be prepared for the table in palatable ways, and that so far as could be judged it was not unwholesome when eaten in quantity.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Lesions in Rabbits Produced by Streptococci from Chronic Alveolar Abscesses.—Noting that there is in the literature no data concerning the result of animal injections with strains of Streptococcus viridans from alveolar abscesses of patients otherwise in perfect health, Moody undertook such a research (*Jour. Infect. Dis.*, 1916, xix, 415). At the outset, the author states that streptococci from all infectious foci should be studied in this manner, in working toward the proof or disproof of the theories of specificity and elective affinity. Strains of Streptococcus viridans were isolated in pure culture from patients with alveolar abscesses. Out of a total of 55 patients, 49 yielded cultures of Streptococcus viridans free from contamination and suitable for injection. The type of organism, other than that it produced green on blood agar, was never determined. No further cultural reactions were undertaken, so that it is impossible to say exactly what organisms were injected. The patients from whom material was obtained were divided into three groups: Group A, those having chronic alveolar abscesses and

"articular rheumatism;" Group B, those having chronic alveolar abscesses and some systemic disorder other than articular rheumatism; Group C, patients having chronic alveolar abscesses, without evidence of any other illness. Four young rabbits averaging 1000 grams in weight were injected with cultures from each case; two received 1.5 to 2 c.c. of a suspension of the sediment from an eighteen- to twenty-hour growth of the original pus in ascites dextrose broth, and two received a similar injection, the latter culture having been obtained by picking typical green colonies from an original blood agar plate to ascites dextrose broth. In all, 178 rabbits were injected in this manner. The rabbits were killed with chloroform after intervals of five to eight days following injection and autopsied immediately and completely. Full notes were taken during the autopsy. The value of these experiments is enhanced by the well maintained constant factors of cultivation —time of the organism, size of dose, and length of life allowed before autopsy. Lesions were found at autopsy in the stomach, muscles, joints, endocardium, kidneys, and jaws. The frequency was in the order named. It was noted that there was a higher percentage of lesions produced in usual areas of localization by strains from cases showing articular rheumatism than from the other groups. Strains from Group B and C frequently produced hemorrhage of the stomach. This very rarely amounted to true ulceration. Hemorrhage, oftenest near the tendinous end, was seen in the muscles. In the joints, suppuration was seen in 44 out of 47 cases. This was the most striking pathological finding at autopsy. Hemorrhage was seen in the endocardium. In only one case was there a well developed vegetative endocarditis, which occurred in conjunction with multiple infarcts of the kidney and spleen. The kidney showed subcapsular and cortical petechial hemorrhages. Marked acute fatty change was often present in the kidney. In the lower jaw marked hemorrhages were seen beneath the incisor teeth and below the periosteum. One animal developed a suppurative cholecystitis from which a pure culture of Streptococcus viridans could be isolated. As a rule, petechial hemorrhages into the mucosa of the gall-bladder were considered as evidence of gall-bladder involvement. The data obtained, when studied, indicated that the Streptococcus viridans, taken as a group and without differentiation may produce lesions in rabbits. These lesions are identical regardless of the source of the organism used. Those strains from patients without systemic diseases developed in rabbits experimentally by cultures from their abscesses is one the author is unable to answer. He feels, however, that specificity or elective affinity cannot be considered as depending entirely upon the microörganism.

A Cutaneous Reaction in Canine Distemper.—Ferry, McGown, Torrey and Rahe proved that canine distemper is due to a bacterium named by them Bacillus bronchisepticus. Kolmer, Harkins and Reichel (*Jour. Immunol.*, 1916, i, 501) prepared a very thick polyvalent emulsion of a seventy-two-hour growth of this organism which they killed by heating to 60° C. for one hour. This emulsion they called bronchisepticin. They used this emulsion in doses of 0.1 c.c. intracutaneously on a large number of dogs. As in other diagnostic skin reactions marked papules, pustules or very marked erythema with

edema were noted as positive reactions. Eye reactions were also tried on the same animals but the results were not satisfactory. Reactions were done on four series of dogs. The first series of nine dogs were suffering from distemper at the time of the test. Of these nine dogs, seven gave a positive and two negative reactions. The second series of twenty dogs were known to have had distemper previous to the tests. Of these twenty dogs, twelve gave positive and eight negative skin reactions. The third series of thirty-seven dogs had no history of infection and it was not known whether they had ever suffered from distemper. Of these animals fourteen gave positive and twenty-three gave negative reactions. The fourth series consisted of eighteen dogs which had been immunized by the use of a vaccine prepared with Bacillus bronchisepticus. Twelve of these eighteen dogs gave a positive and six gave a negative reaction. Some of these dogs had several attacks of distemper and between the attacks the skin test varied and gave no indication as to the dogs' susceptibility. Owing to the inconclusiveness of these figures the authors make no positive claims as to the efficiency of their bronchisepticin antigen as a diagnostic measure, though they believe that owing to the high percentage of positive reactions in dogs having a history of distemper the antigen may be of value. They state, however, that even though it has some value in this way, there is no indication as to the index of the immunity to Bacillus bronchisepticus infections.

Renal Tumors in the Rabbit.—Tumors of any kind are quite unusual in the rabbit. Bell and Henrici (*Jour. Cancer Research*, 1916, i, 157) have found reports of 35 tumors of which 24 were uterine; the remaining 11 were found in lung, stomach, mammary gland, skin and two from kidney. Although tumor development is unusual in the rabbit, the authors found a renal tumor in each of two rabbits on the same afternoon. However, these were the only tumors they have ever observed in some 400 animals. The newgrowths arose from cortical tissue and contained structures characteristic of this tissue. Remains of tubules and, in one instance, the presence of glomeruli were still to be made out. Besides this a less definite and embryonic grouping of cells made up the intervening areas. There were no metastases. A similar tumor was reported by Nürnberger. The name nephroblastoma is suggested for this type.

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THE

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ORIGINAL ARTICLES

CHEMOTHERAPY IN TUBERCULOSIS.[1]

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In its previous lectures on the general subject of tuberculosis the Harvey Society has been especially fortunate.

Speaking on the subject of tuberculosis in 1906, Theobald Smith said, "The present-day problems in tuberculosis which can be approached by experimental or at least by laboratory methods manifest themselves in three different ways:

"1. In the somewhat chaotic condition of opinion concerning the avenues through which tubercle bacilli gain a foothold in the body.

"2. In the wide divergence of opinion concerning the relation of bovine to human tuberculosis.

"3. In the general trend of studies toward the problem of specific immunity, with especial reference to prevention and treatment."

He presented and critically considered the evidence bearing on the portals of entry of the tubercle bacillus and laid stress on the major significance of the direct infection of the lung and associated lymph nodes by way of the inspired air.

Two years later Calmette presented a great deal of material bearing on the proposition that the tubercle bacillus gains its entry

[1] Lecture delivered before the Harvey Society of New York, November 25, 1916.

chiefly through the intestinal mucosa. Today opinion on these subjects is perhaps little less chaotic than at the time of these lectures, but the debate has largely subsided, due to a paucity of competent new evidence.

As the result of exhaustive experimental work in this country and abroad the relation between bovine and human tuberculosis may be considered to be established.

The third group of problems considered by Theobald Smith has been continuously attacked in the interim. The accomplishments of the period were summarized in able fashion by Baldwin two years ago. While immunization has so far led to no practical result in tuberculosis, we should not consider for a moment that the possibilities are exhausted. In the abstract, immunization in some form—active immunization as a preventive measure or combined passive and active immunization during the course of the disease as a therapeutic procedure—most closely simulates nature's own method. If in tuberculosis we have so far achieved no appreciable success along these lines it is doubtless that success awaits some new technical departure adapted to the exact situation, a development that may come with a fresh point of view derived from the study of some other more or less distant disease or which may more probably come as a matter of direct attack if the search is pursued with energy and in a spirit of independent inquiry.

Turning to the subject of chemotherapy in tuberculosis it should be plain that the term is used here and can only be advantageously used in the restricted sense in which it was introduced and employed by Ehrlich—not easy of concise definition—but conveying the implication of biological experimentation carefully coördinated with constructive chemical manipulation, and even, if necessary, chemical research of a most advanced type. This use of the term is emphasized because of late the word chemotherapy has become fashionable as applied to the empirical therapeutic use of any chemical substance from arsenic for gastric ulcer to zinc sulphate for dysentery; a use chiefly designed to conceal an utter absence of either thought or intelligent experimentation. Employing the term in the restricted sense I hope to do little more than to show that it may be properly employed in connection with research in tuberculosis. Even in this I can barely carry conviction as measured by any definite success in the treatment of experimental tuberculosis.

Historical considerations, on the other hand, would allow to the worker in tuberculosis, a certain proprietary freedom in the employment of this word, and especially the real conception it represents. Ehrlich once stated that he counted as most memorable the evening on which he heard Robert Koch describe to the Berlin Physiological Society his researches culminating in the discovery of the

tubercle bacillus.[2] Koch after this discovery at once applied himself with characteristic vigor to the discovery of a disinfectant which should act to rid the body of this destructive invader. The idea of a chemical disinfection of the body was prominent in the early writings of von Behring. As Behring and Ehrlich were at this time most closely associated with Koch (it was Ehrlich who first showed how the tubercle bacillus could be easily stained), who can doubt that this idea was a dominant one and shared more or less equally by all three in those days. All were involved, each in his separate way, in the epoch-making discoveries in the realm of immunization, the theoretical development of serum therapy and its practical employment. Ehrlich alone persisted in the original idea, and finally achieved a surpassing success. This early idea then of a chemical disinfection of the body, let us examine it somewhat more closely as to what it was at its inception supposed to involve—and then see what of an essential nature had to be added to it in order to arrive at a successful result.

In Koch's writings, and in those of v. Behring of somewhat later date, it was considered possible that any disinfectant might probably act in a favorable way on bacterial infection. Many substances were examined for their disinfectant action and those found active in this sense were tried on the animal in the face of the experimental disease. Koch soon emphasized as an *a priori* consideration, the probability that a substance need not actually kill the bacteria in the body; if it would only restrain the growth of the parasite, the natural body defenses might be sufficiently aided so that cure could be attained. But even with this limitation every attempt resulted in disappointment, the stumbling-block apparently being the relatively high toxicity of the chemicals tried for the complex host as against the more limited organization of the parasite.

In a paper by Boer,[3] an assistant of Behring's in this early period, is found the germ of a most important development of this early and rather crude conception. Boer found in the course of an examination of a series of substances for their disinfectant action against a number of species of bacteria that most of them acted with a certain intensity which was of equal value against all the bacteria tried. Thus, phenol is weaker than bichloride of mercury and is weaker in the same degree no matter which microörganism is used as a test object. Methyl violet, on the contrary, was found to be seven times more active against B. anthracis than against B.

[2] "Es war in einem kleinem Raum der Physiologischen Instituts, als Koch in schlichten und klaren Worten unter Vorlegung zahlloser Präparate und Beweisstücke die Atiologie der Tuberkulose mit überzeugender Kraft darlegte. Jeder, der diesem Vortrage beigewohnt hatte, war ergriffen, und ich muss sagen, dass mir jener Abend stets also mein grösstes wissenschaftliches Erlebnis in Erinnerung geblieben ist." Ehrlich, Robert Koch, Frankfurter Zeitzung, June 2, 1910.

[3] Behring, Gesammelte Abhandlungen, Leipzig, 1893, p. 198.

diphtheria. These two bacterial species being equally susceptible to phenol, mercuric chloride and a number of other common disinfectants it is evident that in a very limited sense methyl violet is a specific disinfectant for B. anthracis.

When Ehrlich after the immunity period again turned his attention to chemical disinfectants he was naturally interested in the study of those substances exhibiting specific activities. Working with Bechold,[4 5 6] he studied a series of halogen derivatives of phenol and naphthol from this point of view. Very striking instances of this "partial specificity" as they designated it were uncovered. Without going into detail, it was shown that rather trivial chemical modifications, could profoundly alter the specific features of disinfectant action. Similar series of closely related chemical compounds have since been studied from the same viewpoint by Jacobs, Heidelberger, Amoss and Bull, at the Rockefeller Institute.

At present work of this nature is somewhat in discredit because of the profound disappointment which has resulted from most attempts to apply substances showing exquisite action in the test-tube to the more complicated situation they face when exposed in the animal body. I believe that such discouragement is premature. We are forced to admit now that which we must have foreseen, that test-tube action and *in vivo* disinfection do not go hand in hand. But of all the guides available to the intimate relation of chemical agent to parasite the study of the specific qualities of disinfectant action is the most logical, and I venture to predict that in due time in some quarter an important success will be credited to the application of this fundamental conception. In fact, if we may accept the report of Schiemann[7] such success has already been achieved in its essentials. It is stated by this observer that salvarsan, showing limited curative properties against experimental infections with the anthrax bacillus and the bacillus of swine erysipelas, has definite specific disinfectant action against these bacteria as contrasted with other species whose infections are not therapeutically influenced.

Let us leave for the moment this question of the application of *in vitro* disinfectants to the problem and turn to the first actual success achieved by Ehrlich in the treatment of an experimental infection. The benzidin dye trypan red was found capable of curing trypanosomatous infection in mice. Trypan red has very little if any action in shortening the life of the trypanosomata when the exposure is made in the test-tube. It therefore became apparent that success in this field could be achieved by leaving aside the

[4] Ztschr. f. Phys. Chemie, 1906, xlvii, 173.
[5] Ztschr. f. Hyg., 1909, lxiv, 113.
[6] Disinfektion, Paul Ehrlich (Festschrift), Jena, 1914, p. 505.
[7] Ztschr. f. Immunitatsforsg., 1914, xxiv, 167.

disinfectant qualities of substance *in vitro* and proceeding at once to the crucial test of the animal experiment with a wide variety of compounds.

If now we ask ourselves why those substances acting as disinfectants in a somewhat specific sense fail to rid the animal body of bacteria, while other substances, hardly disinfectants in any sense, are therapeutically active in a more or less specific way, the answer is in part obvious and involves important principles which must be kept constantly in mind in all chemotherapeutic experimentation. When substances active *in vitro* fail *in vivo* it is frequently because they are so distributed when introduced into the animal body that they fail to come in contact with the parasite at all. The substance is quickly eliminated in some cases, is quickly and completely destroyed in other cases, has in still other instances higher affinities for the constituents of the body fluids or cells than it has for the microörganism in question, affinities which may or may not be put in evidence by actual acute or chronic intoxication. When, on the other hand, apparently indifferent substances are found to be therapeutically active it is because in the chemical melting-pot of the animal body, new compounds, active and with the required distribution coefficient, are produced either from the substance itself or under its influence. These two series of qualities of substance, their capacity for specific antiparasitic action and their relation to the complexities of the animal body as evidenced by what can be found out or inferred in regard to their distribution in the body, are basic in the conception of chemotherapy.

When in any particular instance an attempt is made to elucidate these fundamental qualities, purely technical questions of decisive importance come into the foreground. Again, a consideration of Ehrlich's work shows most clearly what is required. It is apparent in the first place that only these diseases can be approached in this way in which the fundamental etiological relationships are cleared up with such results that we are left with a very precise method of experimentation involving in the animal the essential features at least of the pathology of the human disease. The trypanosomiases as studied by Ehrlich are almost ideal from this point of view. The local lesions in tissues are not prominent, the infection can be made to run a rapid and invariable course, the progress of the disease can be precisely followed from day to day by a very simple microscopic examination of the blood, and the animals of choice are small and inexpensive to purchase and maintain. If these cases are defective —and I think they are in some measure—it is in that the pathology of the experimental disease localization of the parasite in particular tissues does not occur as it frequently does in the spontaneous disease, and there is little local tissue reaction. Questions involving the distribution of the chemical agents are consequently much more simple. It is possibly because of this fact that the experi-

mental results have not been duplicated in a striking way in their practical therapeutic application to such conditions as sleeping sickness.

Finally, in the person, in the surpassing mental attainments, of Ehrlich another essential limitation to this form of experimentation was overcome. Coöperation so essential to achievement in every walk of modern life is more apt to materialize as between the various functional units of one man's mind than as between individuals. The united efforts of a trained chemist and a highly accomplished biologist were assured beyond possibility of even temporarily strained relations by the peculiar qualifications of this man of genius. The progress of chemotherapeutic research is contingent on a similar happy conjunction in the human mind and hands of accomplishments in these widely separated fields of research. Whether the limitation which the subject faces in consequence will in the future be surmounted by activity of individuals trained in selected parts of both fields or by the mutual and coöperative activity of specialists in the separate sciences can only be left to the chances of the future.

Having so far considered the place of chemotherapy as related to the various other possibilities of research in tuberculosis, I turn to the immediate subject of the hour. I wish very briefly to consider the facts of experimental tuberculosis in order to show what are its disadvantages and its advantages as a basis for chemotherapeutic study.

The tubercle bacillus as cultivated in the laboratory occurs in three types showing constant qualities: the human, the bovine, and the avian. With the latter we are not now concerned. With either the human or the bovine type, most warm-blooded animals, all those certainly that are commonly used in the laboratory, may be infected and the infection will run a regular course, terminating in death in many instances. The experimental disease certainly involves the essential features of the human disease. At first sight, then, the requisite conditions underlying therapeutic experimentation are already at hand. I say at first sight because, in the minds of the general medical public and those laboratory workers whose experience with tuberculosis is casual, relative certainty of result speaking generally, has been exalted to an almost mythical conception of absolute certainty in each particular case, a fundamental misconception responsible for disappointing mistakes and perhaps actual harm.

Any single culture of the tubercle bacillus is a relatively constant quantity; but, as in all other species of pathogenic bacteria, individual cultures differ in particulars which are of critical value when they are to be used for advanced experimentation. Attempts to modify the properties of particular cultures in any given or constant direction as a matter of controlled experiment have for the most

part failed, yet over periods of years and due to conditions accidentally arising a culture may profoundly change its qualities. Thus, Krause has recently conducted certain experiments which depended upon his possession in the laboratories at Saranac Lake of cultures showing constant differences in virulence, particularly one which now produces in guinea-pigs a disease which progresses for a period and then tends to heal spontaneously. With any given culture at a given time the amount inoculated and the manner in which the inoculation is made are of decisive importance to the result. With a certain culture of human type in a recent experiment of my own, $\frac{1}{10}$ mg. was inoculated intraperitonially into 15 guinea-pigs. The first of these died in eighteen days, the fourteenth died on the thirty-sixth day, and the last one lingered until the sixty-fifth day. In a subsequent experiment 14 guinea-pigs were inoculated in the same way with one-half the amount of the same culture ($\frac{1}{20}$ mg.). Of these the first died on the twentieth day; 8 were alive on the fortieth day; 4 remained on the sixtieth day; 2 still live on the ninetieth day. If the amount of this culture inoculated were still further reduced we would doubtless come to a point when some animals would die and some would live for an indefinite time or perhaps recover entirely from the disease. By inoculating larger doses of this culture no doubt it would be possible to arrange an experiment in which all of the animals would be dead by the end of four weeks.

These results, conversely stated, emphasize the fact that with the same amount of culture inoculated in the same way there is a great variation in the length of time the animals may be expected to survive. With guinea-pigs I have yet to conduct such an experiment in which the last animal did not live at least twice as long as the first to die, and often the difference is much greater than this. If the inoculation is made subcutaneously this variation is increased. If it is made intravenously in guinea-pigs it is apparently not greatly, if at all, diminished. By attention to the weight and age of the animals the variability in result as to individuals is kept at a minimum, but it is always a large factor. These facts make it plain that any experiment designed to test the therapeutic activity of a substance must be so arranged as to permit of statistical interpretation finally. The probable individual variation must be completely accounted for in each experiment. This means that a considerable number of animals must be used for each substance brought under consideration and at least as many for the requisite checks. Just how large this unit group should be has probably not been satisfactorily determined even yet.

You will have noted that the actual time involved is considerable. Thirty days is no short period and ninety days is one-third of the conventional laboratory year. Contrast this with the four days of the typical animal experiment in Ehrlich's work with trypanosomata

and it is self-evident that we have here a very distinct handicap on the application of the chemotherapeutic idea to tuberculosis work.

Efforts have been repeatedly made to discount in whole or in part the variation in the length of time animals live after such inoculations by terminating the experiment on a certain date through slaughter and postmortem examination. Postmortem examination of the animals dying spontaneously reveals a variation in the exact condition of the organs which is fully as great and in my opinion considerably greater than that shown in the length of life in days. One animal dies because the liver is completely degenerated, another because the lungs are consolidated, a third is drowned in his own fluids, showing more or less local disease widely distributed, an intense edema of the lungs and the pleural cavities completely filled with fluid exudate. These conditions, if they are to be interpreted, must also be considered statistically, and this if it is to be done must involve an even larger material than when the resistance of the animal is accounted for as a single factor. Such attempts at a short cut on any scale so far attempted are quite unsound. In any experiment, after all of a sufficient group of controls are dead and accounted for, not before then, a considerable amount of guidance may in the future be obtained from the condition of the organs of killed or dying animals.

Similarly, reliance has been placed on the presence or absence of large numbers of tubercle bacilli in the lesions or apparently healthy tissues of animals dying within the period of life of controls. If an animal dying in this period shows few lesions or none, and if tubercle bacilli are found only in small numbers, it may sometimes be safe to conclude that death was not due to tuberculosis and the animal can properly be excluded from consideration. But in the presence of moderately extensive lesions it must be assumed that an animal may be as apt to die from the consequences of a largely successful effort to remove bacilli, as from the presence of the microörganism *per se*. After the last control has died the presence or absence of bacilli may have great significance in the experiment. Previous to that time, at least until much more extensive observations as to the variability of this factor have been made, opinion based on this point has no value.

Two things then, the absolute time involved in each experiment and the size of the experiment, as conditioned by the number of animals which must be used to cover individual variations, are the essential factors of difficulty that stand in the way of the application of the principles previously considered to tuberculosis as an experimental disease. Can the difficulties so imposed be directly overcome? As abstractions, very easily; as a practical matter it may easily involve a concentration of trained effort and an expenditure of money beyond that so far applied to the study of any single problem in medical science to assure an even chance of success.

It has seemed to me quite possible that the issue presented might be treated by avoiding it. I have spent a considerable amount of time in the study of various forms of local tuberculosis and of general tuberculosis in animals other than the usual guinea-pigs and rabbits, in the hope of encountering a form of the disease which would be less variable or run a shorter course than I have indicated. Most hopeful for a time seemed the study of a tuberculosis of the cornea in rabbits. With Dr. Montgomery I studied rather more in detail this interesting local disease than had previously been done. On a small scale it seemed ideal for our purpose. When, however, the test came to be made more largely it was found that the individual variation in reaction was as great as in other forms of experiment and that certain other factors were introduced which added to the difficulty. We were dealing here with an open lesion, and this very frequently became infected with extraneous organisms. Moreover, there is a constant discharge of bacilli from the purulent conjunctival sac, and unless the experiments can be segregated, the animals being cared for by already tuberculous persons, there is the constant likelihood of complicating other experiments in progress and a continuous menace to the health of one's employees. The possibilities of similar studies of other lesions or of the disease in other animals are not at all exhausted and such efforts should prove profitable in the future.

Offsetting the disadvantages which have been pointed out as inherent, tuberculosis offers an interesting opportunity quite peculiar to itself. The multiplication of the bacillus in typical instances is accompanied by a local rearrangement of the body cells to form nodular lesions readily visible to the naked eye and of characteristic structure microscopically. These nodules, the tubercles, can be used as a guide in the study of the distribution of extraneous chemical compounds to the neighborhood at least of the bacteria. The tubercles, if necessary, can be picked out and examined chemically, or more practically, for a beginning, colored substances can be chosen as the starting-point of combined chemical and biological research. These can, under favorable circumstances, be immediately recognized in the tissues, and questions of distribution can be rapidly answered by their use.

On the occasion of a visit to Baltimore four years ago I was shown some very beautiful preparations by Dr. Winternitz, preparations made in a study of the origin of the cells taking part in the reaction of the earliest hours after an infection of the animal with tubercle bacilli, and since carefully described by Bowman, Winternitz, and Evans.[8] My interest was aroused in the possibility of making a wider application of the so-called vital stains, and I shortly found by experiment that the fibrocaseous tubercle took up certain of

[8] Centralbl. f. Bkt., 1912, I Orig., lxv, 403.

these stains in a characteristic way. The results of these early experiments were recorded and summarized in the following terms:

"The first of these experiments shows again the selective action of Isaminblau for the large mononuclear phagocytic cell as pointed out by Goldman. These cells are found abundantly in the peripheral portions of fibroid tubercles.

"The second experiment is of great interest, showing, as it does conclusively, that extraneous chemical substances of proper constitution may within a few days penetrate to the caseous centre of a tuberculous mass and become concentrated there in greater degree than in the normal surrounding tissues. The particular substance used in this experiment, trypanroth, may probably be without effect on the lesion itself, but the result should be a great stimulus to the future work in a similar direction."[9]

These experiments seemed to me to be of the utmost importance as a basis for further experimental work of a coördinated chemical and biological nature. The opinion had been quite generally expressed that as the tuberculous tissue was without internal blood supply it could be reached only with difficulty if at all by medicinal agents which might be made to circulate in the blood stream. Such an opinion, if to decisive weight, would make it appear to be an unreasonable waste to experiment largely with the idea of developing general medicines which might be hoped to influence the local tuberculous process. The actual result, on the contrary, rendered such experimentation reasonable, and, as it seemed to us, eminently desirable.

DeWitt[10] in this country and v. Linden[11] abroad reported somewhat later on similar observations made independently with methylene blue. DeWitt confirmed my particular observations, reported on a number of dyes which failed to appear in the tubercle, and added trypan blue to the list of penetrating substances. I have since found, in the course of observations, so far unpublished for the most part, that a considerable number of azo dyes related in their chemical constitution to trypan red and trypan blue penetrate the tubercle in this way. DeWitt has since used methylene blue as the starting-point for a series of studies intended to serve the same purpose as those I am about to consider.

These observations served as the starting-point of a series of researches in our laboratory which are being continued at the present time with the object of finding or building up substances which shall have this penetrating quality well developed, and which shall at the same time be possessed of physiological activity of such nature that they might be expected to act favorably on the tuberculous process. If this effort should result in any measure of success the

[9] Arch. Int. Med., 1912, x, 68.
[10] Jour. Infect. Dis., 1913, xii, 68.
[11] Beitrage z. Klinik d. Tuberkulose, 1915, xxxiv, 1.

credit would be shared by me with Mr. Robert B. Krauss, who has been continuously associated with me for four years, and who has been responsible for all of the purely chemical work carried out.

The first concrete problem outlined on the basis of the considerations above outlined was to take the dye trypanroth, which had been used in the more striking of the experiments commented on, and try by chemical manipulation to form from it, or with it, a substance having physiological activity while preserving the qualities which enabled the dye to penetrate the tubercle.

Mr. Krauss undertook to make as many modifications of trypan red as he could, following certain general lines.

1. The staining qualities of the substances were to be at least in part preserved.

2. The preference was to be given to substances containing iodin, phenolic substances, or certain other constituents.

These specifications were drawn up on very general grounds, some of which may be stated as follows: Iodin was selected because of the long-standing belief among medical men that iodin was of some favorable influence on the progress of tuberculosis when applied locally either as an element or as iodoform; carbolic acid, guaiacol, and other phenolic substances were known to be relatively active disinfectants against the tubercle bacillus, and some of them also enjoyed a reputation as medicines for this disease. The staining qualities were to be preserved as far as possible as a guide to the localization in the course of the subsequent animal experimentation.

The chemical work involved was successful. In the course of a year and a half about seventy-five compounds were secured on the plan outlined. The chemical manipulations and results were published by Krauss.[12] These preparations were used in a preliminary way in animal experiments and some interesting observations were made. In general it was indicated that none of the substances exerted any curative influence on experimental tuberculosis. Some of them seemed, however, to have a definite influence on the vigor and rate of the formation of bloodvessels and connective tissue in and around the tuberculous process, the tests being made on the rabbit cornea.

The plan had been to prepare enough of each substance for a moderate amount of preliminary experimentation and then to make again those which seemed useful for further work. About the time the preliminary study of these compounds was completed the war arose and necessitated a change of plan. We had been purchasing trypan red from abroad and further regular supply was cut off. What was on hand and the occasional lots since secured we have used in a study, so far uncompleted, of the composition of the substance with view to its manufacture.

[12] Jour. Am. Chem. Soc., 1914, xxxvi, 961.

I have already said that following our observation that the tuberculous tissue in the living animal was easily penetrated by trypan red, many other dyes of the same general class, chemically speaking, were tested for their reaction in this particular. A considerable number were found which could become concentrated in the diseased tissue to a greater or less extent. Many of these had never been accurately described from a chemical point of view, others presented difficulty of manufacture beyond our means. After much consideration a dye known to the trade as Niagara blue 2B (benzidin + 2H acid) was chosen as the starting-point of a second attempt to construct a series of iodin and phenol compounds. It has been necessary, owing to the state of the market, for us to build up this substance from the raw products. This has been accomplished and a considerable series of compounds made by adding iodin and phenolic substances to Niagara blue have been studied, with rather meager results, which I shall not comment on now.

Covering about the same period of time as these studies on the relation of the vital stains to the diseased tissue, and in the hope of acquiring information which should in some measure guide that work, we have been studying the disinfectant action of various substances for the tubercle bacillus. We have hoped to uncover substances having the partially specific action discussed in the earlier paragraphs of this paper. Much time has been spent over methods. The procedure by which the results here considered were obtained was to determine the least concentration of the substance in glycerin-boullion, which would definitely inhibit the growth of the tubercle bacillus.

Because of the relation to the work outlined in considering the subject of the vital stains, we have so far paid particular attention to anilin dyes. We have also considered the more common disinfectants and some substances which are used in the building-up dyes. In order to get an idea of the specific qualities of the inhibiting action of the substances tested the typhoid bacillus was at first used in comparison with the tubercle bacillus. Very recently in the course of some work being carried out for the Pneumonia Commission of the city of Philadelphia I have gone over the whole field again, using the pneumococcus and staphylococcus aureus. Several hundred substances have in this way been examined with the following general results:

I. The growth of the typhoid bacillus is, with few exceptions, if any, less readily inhibited by anilin dyes than that of the pneumococcus, staphylococcus aureus, or the tubercle bacillus.

II. The triphenylmethane dyes, as a group, inhibit the growth of the pneumococcus and staphylococcus in dilutions which do not inhibit the tubercle bacillus. Among themselves these dyes vary greatly in the concentrations at which the four species are affected, both absolutely and relatively.

III. The azo dyes as a group inhibit the growth of the tubercle bacillus more readily than that of either pneumococcus or staphylococcus aureus. Again, there is a great relative and absolute variation in the effective concentrations. In the extreme instances in this group the tubercle bacillus is one or two hundred times as susceptible as the pneumococcus, and it seems proper to consider that the inhibitory power is in large measure specific.

IV. The other great groups of dyes give less striking results, the oxazines and thiazines, to which methylene blue belongs, are more active against the cocci; the eurhodines, with neutral red as an example, are more effective against the tubercle bacillus.

Certain other points developed by this work deserve passing mention. Many dyes, the majority perhaps, stain the growing membrane of the tubercle bacillus with greater or less intensity. The inhibitory power of the dyes is not at all, however, a function of this capacity to stain the membrane, nor is it a function of any particular staining quality of the dyes for silk, wool, or cotton, so far as we have been able to determine up to the present; nor of the solubility of the dye in alcohol or oil as compared to water. A small amount of work so far carried out indicates that among organic compounds other than the dyes, substances exist showing the same variable capacity to restrain the growth of the tubercle bacillus. Also a very limited number of experiments indicate that this capacity to restrain growth is not directly related according to any uniform or simple rule to the true disinfectant or lethal action of substances. Much more work will be required before these observations can be interpreted in terms of previous work with disinfectants.

Thus, approaching our problem from one point of view we have found a number of substances capable of penetrating tuberculous tissue and consequently having, as it seems to us, at least a slightly better chance of acting as antibacterial agents in tuberculosis than those which cannot so penetrate the diseased tissue. From another point of view we have found many substances possessing in marked degree and in a partially specific way the ability to greatly restrain the growth of the tubercle bacillus in the very limited conditions of the test-tube.

It has for some time back been a matter of serious effort with us to bring these two sets of qualities together in the same substance. We have had a definite though limited success in this effort. The dye Niagara blue 2B can be made to enter into chemical combination with various substances, iodin, phenol, certain fatty acids, and the like. The resulting products are apparently definite chemical compounds. As a rule they are dyes and with properties noticeably different in one or more particulars from the original substance. As a general thing the inhibitory capacity against the cultures is distinctly increased; the capacity to enter the tuberculous tissue is, on the contrary, usually lost entirely or greatly

diminished. In one instance so far a condensation product of Niagara blue with formic acid, the partially specific inhibitory value, is raised about twenty times, from $\frac{1}{5000}$ to $\frac{1}{100000}$ the staining qualities for tuberculous tissues being in large measure retained.

Again, in studying the inhibitory power of various dyes, Mr. Krauss has constructed a long series of compounds, not new in principle, but for the most part never before made, according to the following scheme: Benzidin monosulphonic acid is so treated as to diazotize its free NH_2 groups. There is then added under proper conditions a quantity of the variant substance calculated to react completely with one of the NH_2 groups. When the reaction is complete there is added sufficient amidonaphtholdisulphonic acid (H) to react completely with the other NH_2 group. In this series we have also encountered a number of dyes possessing distinct inhibitory powers. Very few members of the series, so far as it has yet been extended, have any staining qualities as applied to the tissues of the living animal. When crude creosote is used as the critical component, however, a mixture of closely related dyes is produced in which both qualities are present in marked degree. These products are violet-blue dyes, staining the connective tissues of the living animal with moderate intensity and penetrating the tubercles very well. The inhibitory power of the mixture is stated in our terminology at 100000 or about one hundred times that of the dyes trypan red and trypan blue, which were the starting-point of our work in this direction. Partial specificity is also manifested by this preparation.

The accomplishments of our laboratory up to the present in the endeavor to study tuberculosis from the chemotherapeutic point of view can then be summarized in a sentence: we have built up several substances which in the test-tube are capable of restraining the growth of the tubercle bacillus in marked and measureably specific degree, and which when injected into the living tuberculous animal are capable of penetrating to the centre of the masses of diseased tissue.

Attractive as may be the plan by which these substances have been reached it would still be only the happiest accident if their further qualities were such as to render them active against the progress of tuberculosis in the animal body. Neither would the failure of two such substances mean that the idea is fruitless. For the present therefore our efforts in the chemical laboratory are directed toward increasing the number of substances possessing these (as it seems to us) fundamentally desirable qualities. We have also turned ourselves seriously to the testing of the possibilities of these substances and their relation as therapeutic agents. The latter phase of our work is scarcely begun and I shall pass it by with but few words.

Drawing on the literature for precedents I may cite the following studies as the most striking of the available examples:

1. Koch and his pupils in repeated experiments during the years 1890–1897 demonstrated that by the use of tuberculin the life of guinea-pigs infected with considerable amounts of pure cultures of the tubercle bacillus could be definitely prolonged. These tuberculin experiments are worthy of the most serious consideration. The same result was reported by a number of different observers at the time and I find no contradictory experiments. The exact chemical nature of tuberculin has never been determined and it is to be presumed that its action comes within the field of immunity reactions rather than that of chemotherapy. I have included this substance in this brief discussion because I believe that the results with it are the best available standard on the basis of which the value of other results may be estimated.

2. Von Linden[13] in 1912 and again in 1915 presented tables showing that by the use of compounds or mixtures containing copper; or copper and methylene blue; or copper, lecithin, and cod-liver oil as a salve, with or without the separate administration of iodized methylene blue, the life of tuberculous guinea-pigs could be prolonged. The results as presented compare favorably with those gotten earlier with tuberculin, but in no way surpass them. Attempts to repeat some of the experiments by Corper in this country failed and Selter abroad has denied their significance.

3. Certain tables published by DeWitt[14] (1914) may be interpreted as evidence that copper and mercury compounds (or salts) of trypan blue can act favorably on the progress of tuberculosis in guinea-pigs, although the author does not put forward any positive claim for them. DeWitt has since stated publicly that she had obtained more definitely favorable results with a mercury compound of methylene blue.

4. Koga[15] (1916) believes he has attained results of value with a compound containing copper and cyanogen. On the face of the evidence again, this substance produces a result comparable to tuberculin but not surpassing it.

5. In the case of the two substances whose development in our hands I have described above, the one, that made by condensing formic acid with Niagara blue, has done only harm in guinea-pig experiments so far. In this it corresponds to Niagara blue itself. The diazo creosote compound seems in preliminary experiments to be capable of extending the period of life of infected guinea-pigs in certain instances. The percentage of animals favorably affected in any series is less than in the tuberculin experiments of Koch's co-workers.

[13] Loc. cit.
[14] Jour. Infect. Dis., 1914, xiv, 498.
[15] Jour. Exp. Med., 1916, xxiv, 107.

Those critically inclined need not search far in the original accounts given of any of these experiments to find ground for denying that they are of significance. Such criticism has been offered and will certainly be continually forthcoming. Insofar as attempts have been made or are being made to introduce any of these substances into the practice of medicine, any amount of skeptical opposition is in my opinion fully warranted. In 1890 it was quite justifiable to take the first favorable results obtained in the laboratory and make careful clinical trial of tuberculin. We should, however, profit by this experience and proceed with great caution in the clinic until the evidence shows that new substances are distinctly better than tuberculin experimentally.

In the interest of scientific progress, on the other hand, all of these results should be treated with great charity. In view of the purely statistical nature of the inquiry, the experiments must be repeated a number of times before they are finally accepted as evidence, but it must be remembered that a single failure has no more interest than a single success. If it be granted as a probability that some measure of the truth may lie in these observations, the future of chemotherapeutic studies in tuberculosis is not discouraging. At this stage of development the possibilities compare favorably in this particular case with those which offered for the broader subject of chemotherapy when Ehrlich was first able to cure trypanosomatous mice with trypan red. Several substances seem now to be known which are capable of giving a slight advantage to the host in its contest with the parasite. This number must be multiplied by empirical search through known chemical compounds, and each such substance showing a suggestive lead must be subjected to carefully considered chemical manipulation to develop to the full its latent possibilities. Each year of the five that I have been actively engaged in this work has seen some added idea or suggestion of real value, and we may be sure that if in the future faith is expressed in continuous experimentation and confidence is put in evidence by financial support adequate to the size of the task in hand the desired result will be achieved.

REFERENCES.

The following books contain matter of the first importance to anyone interested in the development of the subject of this lecture or related questions:

1. Gesammelte Werke von Robert Koch, Leipzig, 1912.
2. Behring, Gesammelte Abhandlungen, Leipzig, 1893.
3. Paul Ehrlich, Jena, 1914.

STRANGULATED RETROPERITONEAL HERNIA INTO THE PARADUODENAL FOSSA; OPERATION; DEATH ON THE NINTH DAY.

By William Parvin Bramlett, M.D.,
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and
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(From the Second Surgical Service of the Episcopal Hospital.)

Retroperitoneal hernia is rarely encountered on the operating table. Up to 1899 Moynihan could find only 57 cases on record of the variety into the left duodenojejunal fossa (to which type the present case belongs), the majority of these having been accidentally found at autopsy, and occurring independently of the disease producing death. Coley[1] says only 10 successful cases of operation have been reported, 9 of left and 1 of right duodenal hernia.

It is not an uncommon occurrence to have two or more of these retroperitoneal fossæ present in the same individual, so that it is difficult to give an accurate description of their boundaries. The folds which form the boundaries are formed in the fetus by the fusion of the left surface of the primitive mesentery of the duodenum with the right surface of the descending mesocolon, and become accentuated by traction made upon this line of fusion by the eventual drifting of the duodenum to the right and of the descending mesocolon toward the left. The fossa which became the seat of hernia in our case, and which is most frequently involved in cases of duodenojejunal hernia is known as the paraduodenal fossa or fossa of Landzert (1872). The fold producing it results from the presence of the inferior mesenteric vein, for which the fold acts as a mesentery. This vein, passing upward from the mesorectum, verges toward the midline on its way to empty into the splenic vein, and in most cases runs entirely retroperitoneally, not raising any fold or reduplication of the peritoneum. When, however, this fold, or *plica venosa* as it is called, is present, it consists of a vertical and a horizontal portion, the vertical being to the left of and below the fossa and the horizontal bounding the fossa above. Just to the left of this vein, the left colic artery is found, running upward from its origin in the inferior mesenteric artery. The lower boundary of the fossa is completed by a serous fold, the mesentericomesocolic fold, which runs from the left side of the mesentery downward and a little laterally to the right side of the upper meso-

[1] Keen's Surgery, 1908, iv, 102.

sigmoid. To the mesial side of the paraduodenal fossa is the root of the mesentery. This paraduodenal fossa, then, is situated to the left of and some distance away from the ascending limb of the duodenum (Fig. 1). Posteriorly it is bounded by the peritoneum covering the psoas muscle, the renal vessels, the ureter, and a portion of the left kidney. Its orifice looks downward and to the right, its cavity upward and to the left. The width of its orifice depends on the distance of the inferior mesenteric vein from the duodenojejunal flexure.

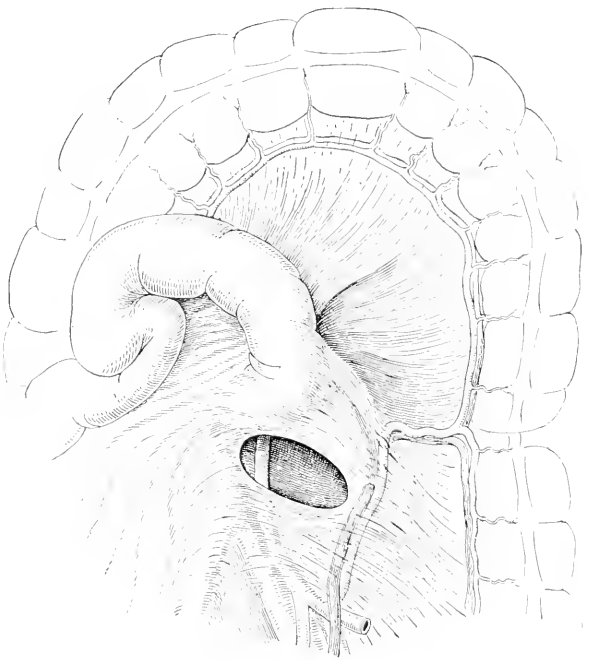

Fig. 1.—The paraduodenal fossa or the left duodeno-jejunal fossa. Note the inferior mesenteric vein and the left colic artery near the left border of the fossa. (After Poirier and Charpy.)

The causes of these herniæ are similar to those which produce other types. The presence of a deep fossa, with tense margins, and intestines which are freely movable, predisposes to the development of such a hernia. Under such circumstances a coil of intestine may be forced into the fossa by violent peristalsis or by the sudden increase of intra-abdominal pressure which follows crying in infancy or sudden strains in adult life. The hernia may develop almost at any age. Moynihan mentions a case in a child, aged fourteen days; and in herniæ which first cause symptoms in adult life, as in our own patient, a man, aged forty-seven years, it is often impossible

to know how long the condition may have existed without causing any symptoms.

In most cases the previous history is negative, though, as in the present case, there may have been attacks of abdominal pain, generally ascribed to "indigestion." The symptoms of strangulation are merely those of intestinal obstruction, and frequently the patient is not seen until peritonitis has developed. If the patient be seen early the physical signs probably are more reliable than the symptoms. While the size of these herniæ varies considerably, they usually are of sufficient size to produce a circumscribed globular fulness which, when small, is located slightly above and to the left of the umbilicus. When they attain their maximum size, however, they may occupy one-third of the abdominal cavity. The prominence formed by the hernia is then especially noticeable in contrast to the flatter area to the right, occupied by the ascending and transverse colon and by the few remaining coils of small intestine not involved in the hernial sac. In this respect they may resemble those cases of intussusception which present Dance's sign. Sometimes, as the hernia increases in size, it may be discovered on palpation, or borborygmi and subjective symptoms may point to the region of the abdomen involved. To palpation, the mass may have either a doughy or a cystic feel, but no wave of fluctuation can be obtained. The statement made by Moynihan that the tumor always yields a sonorous note on percussion and clear intestinal sounds on auscultation, no doubt may be true in nearly all cases seen early, particularly when no strangulation is present; but in our own patient all intestinal sounds were absent, owing to beginning peritonitis; and the percussion note was dull, which may be explained by the presence of free fluid outside of the hernial sac and by the accumulation inside the intestines within the sac of three enemas which had not been expelled.

Other physical signs which are said to occur are the presence of hemorrhoids from obstruction of the inferior mesenteric vein in the neck of the sac, and also a dilatation of the superficial abdominal veins serving as anastomosis between the epigastric and mammary.

On opening the abdomen a large globular mass is seen, situated to the left of the lumbar vertebræ. This mass is neither cystic nor hard and nodular, but is doughy in consistency, and the coils of intestine can be palpated beneath the smooth peritoneal covering of the sac. The colon retains its normal relationships, with the exception of the descending portion, which is pushed far to the left side. The entire small intestine may be within the hernial sac, in which case the only coil emerging from the sac is that nearest the cecum. Some cases have shown coils of small intestine to enter and to leave the sac, thence to reënter and again to leave it. The case herewith reported showed a few coils of upper jejunum lying outside the sac, while the duodenojejunal flexure itself, and all

the rest of the jejunum and the ileum, to within a few inches of the cecum, formed the contents of the hernial sac. The loops of intestine lying outside the sac, if there be obstruction, as in our own case, will be much distended; and after strangulation has existed for a number of hours, free abdominal fluid will be present.

The most plausible explanation for the enormous size of some of these herniæ is that the lower portion of the gut is the first to enter the sac, and that the remainder of the intestinal tube is carried into the sac by peristalsis, just as in an intussusception the intussusceptum is carried into the intussuscipiens. If the orifice of the sac be large, and if peristalsis be violent, portions of the interned gut may be forced out from time to time; or perhaps several widely separated loops of intestine may be involved from the beginning. Either of these factors would explain the condition in which portions of gut are seen to enter, leave, and again enter the sac. It, therefore follows that in reducing these herniæ at operation, traction should be made on the highest portion of gut involved, as it will be found this has been the last to enter. It also follows that the lowest portion of bowel involved is most apt to be the seat of strangulation; although this may arise at any part from the presence of adhesions or kinks, or from constriction at the orifice of the sac.

The enormous size of some of these herniæ has already been mentioned. Cases measuring as little as 1.5 x 2.5 cm. are on record, while others have been reported measuring 14.5 x 24.5 cm., the larger measurement being in the longitudinal axis of the body. In the present case no accurate measurement was possible; but it is sufficient to say that the sac appeared the size of a football, and filled about one-third of the entire abdominal cavity. These herniæ spread upward into the transverse mesocolon, outward toward the descending mesocolon, or outward and downward, as in the present case.

The sac may be described as a pocket in the peritoneum. It consists of a single layer of peritoneum in itself: The posterior surface rests upon the retroperitoneal structures while the anterior layer lies in contact with the posterior surface of the posterior parietal peritoneum, giving us two peritoneal layers anterior to the contents of the sac. The orifice of the sac, like the hernial mass, varies greatly in size. In the recorded cases the breadth has measured from 3.5 to 6.5 cm. and the length from 1.5 to 13 cm. In our case the diameter of the orifice was about 5 cm.; after incision of the constricting margin it was easy to introduce the entire hand into the sac.

In the treatment of these herniæ it is especially important to bear in mind the structures which run in the anterior wall of the sac, at or near its free margin, namely, the inferior mesenteric vein and the left colic artery. It is often necessary to relieve the strangulation before the hernia can be reduced; and when the vein lies close to the

orifice the only place at which an incision can be safely made is at the lower border of the constriction through the mesenterico-mesocolic fold, keeping to the mesial side of the vein. In all cases careful palpation should be made for the location of these vessels and injury to them avoided. After relief of the strangulation the hernia should be reduced as described above, beginning with the uppermost loop of intestine. After reduction the intestines are to be treated as in other cases of strangulated hernia. Finally attention must be paid to the retroperitoneal sac, which will predispose to a recurrence of the hernia if nothing is done to prevent such a sequel. The simplest method of disposing of the sac is to close its orifice by sutures, sewing the free anterior margin to the posterior parietal peritoneum which covers the psoas muscle, etc. This is what was done in our case, owing to the poor condition of the patient. There are, however, two objections to this procedure; the first was shown in our case at autopsy ten days after operation, when the suture of chromic catgut was beginning to be absorbed, and the two peritoneal surfaces had not become tightly adherent, thus opening a way for a recurrence of the hernia. The second objection is the danger of cyst formation in this walled-off sac. The operation of choice, therefore, though only applicable when the patient's condition warrants a rather prolonged operation, is to excise the entire sac and then to suture the remaining two edges of peritoneum. In either operation the inferior mesenteric vein is constantly in danger of injury. And though its division and ligation, or even a similar treatment of the ascending branch of the left colic artery, might not entail a fatal result, injury to either would subject the patient to much risk, and considerably complicate the operation.

Case History. Arthur C., aged forty-seven years, a laborer by occupation, was admitted to Dr. Frazier's service in the Episcopal Hospital, Philadelphia, September 25, 1915; discharged October 6, 1915 (died).

Family History. Negative.

Previous History. For years the man has had attacks of cramp-like pain in the upper abdomen. One especially severe attack occurred about eight years ago, but he recovered without operation. These attacks seem to occur more frequently after eating steak or crabmeat. Vomiting occurs and is followed by relief of the pain. The bowels are not constipated during these attacks, but move regularly once daily. Between these attacks the patient had been troubled at times by morning gagging; he does not know what causes this, but admits that in addition to the use of tobacco and the milder beverages, such as tea and coffee, he has always been a heavy drinker of beer. He has done heavy laboring work all his life.

Present Illness. The chief complaint is intense abdominal pain. The present condition began about sixteen hours previous to admis-

sion, with severe cramp-like pain in the upper abdomen. This came on him suddenly while at work, about 8 o'clock in the morning, and has continued without relief. The pain has remained generalized over the upper abdomen. Shortly after the onset of the pain he vomited a small amount of clear fluid. Vomiting has been repeated seven or eight times, and on the last occasion the vomitus was dark in color. Before admission to the hospital he was given three enemas by his physician; none of these were expelled. On admission he said his pain was somewhat relieved.

Physical Examination. The patient is well nourished and does not appear older than his given age. Inspection of the eyes shows a bilateral coloboma, which he states is congenital. Aside from this abnormality, the face, head, and neck are negative, as is the heart. Auscultation over the lungs, however, reveals an occasional rale at each base on deep inspiration. The abdomen is symmetrically distended; its walls are muscular, and there is no dilatation of the superficial veins. There is marked generalized rigidity, making palpation of the various organs or abnormal masses impossible. Palpation is painful over the entire abdomen, but especially marked above and to the left of the umbilicus. There is a peculiar doughy or cystic sensation to the palpating hand, different from that usually obtained in cases of peritonitis. On percussion the note seems unusually dull for gaseous distention, but no fluid wave can be obtained. The liver dulness appears to be about normal, though it cannot be accurately outlined. There is entire absence of peristaltic sounds. Examination of the extremities and external genitalia was negative. The white-blood cells numbered 18,000.

The patient was admitted to the hospital at midnight and refused to have any operation done. His vomiting continued, and by the following morning the vomitus was quite dark in color and was beginning to have a fecal odor. A second blood count showed 17,680 white-blood cells, with 88 per cent. polymorphonuclears.

Operation. Between 1 and 2 o'clock in the afternoon of the day after admission, and thirty hours after the onset of his acute condition, the patient finally gave his consent for operation, which was immediately performed. At this time the abdomen was immensely distended and tense; there was dulness all over, except under the left lower ribs, the tympany here being due to the stomach. There was great tenderness everywhere. No peristalsis was audible. No definite diagnosis was made,[2] but it was noted that "if this is peritonitis, there must be a quantity of pus under tension."

Nitrous oxide and ether were used for anesthesia, both of which were taken poorly. A right rectus (paramedian) incision was made in the epigastric and umbilical regions, the incision being enlarged subsequently to a length of 17 cm. (7 inches). Bloody serum

[2] The diagnosis on admission was "perforated duodenal ulcer."

poured out on opening the peritoneal cavity. (No growth was obtained from its culture.) A few coils of obstructed small intestine lay in the right kidney pouch, distended to 7.5 cm. in diameter, and almost black. No coils of intestine tended to protrude, and in spite of the large abdominal wound it was impossible to deliver those seen. The hand, introduced, felt a large cystic mass as large as a football in the center of the abdomen, and a few coils of collapsed intestine to the left and in the pelvis. These were evidently the

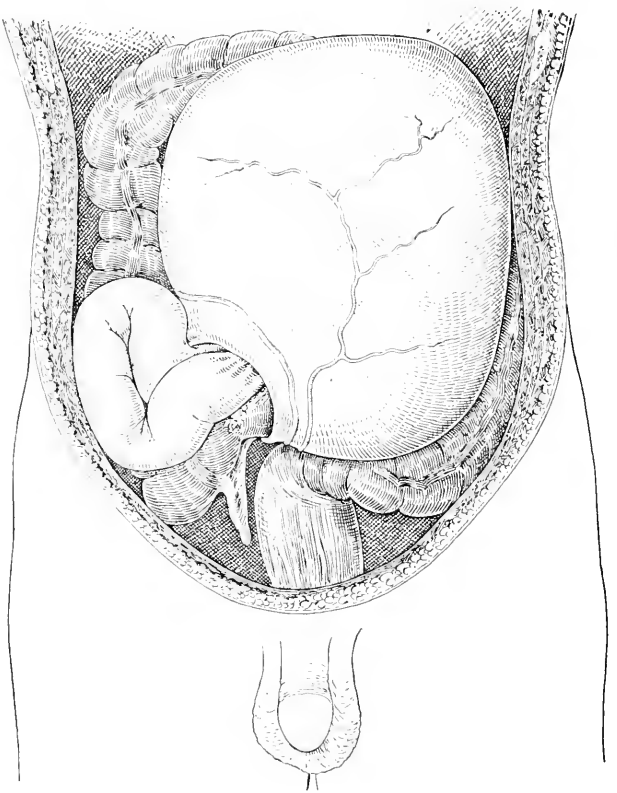

Fig. 2.—Diagram of a case of strangulated retroperitoneal hernia into the paraduodenal fossa.

descending colon and sigmoid. The liver, stomach, and pylorus could be felt in their normal positions above the mass. It was quite evident that all the small intestines, with the exception of the few obstructed coils first encountered, had entered a retroperitoneal hernia and were strangulated (Fig. 2). The entire mass was then delivered through the abdominal incision by depressing the abdominal walls around it. The orifice of the sac could now be seen, about 5 cm. in diameter, on the right side of the mass, the intestines

having entered from the right and travelled toward the left. As no important bloodvessel could be detected in the constricting ring, its anterior margin was divided for about 1 cm. The coils of intestine contained in the sac were then easily delivered, beginning at the upper end. All these coils were distended and congested, but unadherent. Their contents evidently consisted of an accumulation of intestinal juices, plus the three unexpelled enemas which had been administered to the patient before his admission to the hospital. The last coil extracted was black and looked almost gangrenous for a distance of 25 to 30 cm. This last coil was continuous, with about 4 cm. of normal intestine, which had not been within the sac, and which appeared to enter the cecum. The upper coils of small intestine which had been within the sac were almost normal, and were directly continuous with the much distended coils of small intestine seen on first entering the abdomen, and lying in the right kidney pouch. These much distended coils in turn were continuous with the duodenojejunal flexure, which lay within the orifice of the sac on its cephalad margin.

The condition of the terminal loop of ileum gave most concern. Upon application of hot saline solution the normal color was partially regained, with the exception of numerous small spots, where it was feared perforations might develop. An anastomosis was considered, but owing to the patient's condition, and the difficulty of finding the large bowel (which was pushed out of sight by the hernial sac), this idea was abandoned. In addition to the damaged condition of the gut itself the bloodvessels in the mesentery of several coils of intestine were thrombosed.

The hernial sac was then explored, the orifice now easily admitting the surgeon's hand. It was found to be an invagination of the posterior parietal peritoneum to the left of the origin of the jejunum, and its entire contents, with the exception of the duodenojejunal flexure (which lay in the office), had been reduced. The free anterior margin of the orifice of the sac was now sutured to the posterior parietal peritoneum, with a continuous suture of No. 2 chromicized catgut. Gauze packs were removed from the abdomen, the intestines replaced, and the abdominal wound closed, without drainage, by means of heavy mass sutures of silkworm gut, passing through all layers of the abdominal wall; the anterior sheath of the rectus muscle was sutured separately with a buried suture of No. 2 chromicized catgut.

Postoperative History. The progress of this case is interesting for the remarkable attempt of nature to restore the abdominal condition to normal.

On the *first day* after operation the patient retained water neither by mouth nor by bowel. He passed no flatus, but the abdomen was only slightly distended.

On the *second day* gastric lavage was necessary both morning and

evening to relieve distention and vomiting. However, 2 pints of water were retained by bowel and about 7 ounces by mouth.

On the *third day* gastric lavage was required once. Four pints of water were retained by bowel, and 10 ounces of broth totalling about 40 calories, by mouth.

On the *fourth day* gastric lavage was required once. Four pints of water and a nutritive enema containing 776 calories were retained by bowel, and 6 ounces of water and small quantities of broth and albumen, totalling about 6 calories, were retained by mouth. Beginning impairment of the percussion note at the base of the right lung was noted today.

On the *fifth day* the abdomen was softer, there was less pain, and the total quantity of vomitus was only 11 ounces. Nourishment of 1552 caloric value was retained by bowel and 18 calories by mouth. The lower third of the incision was infected. A clean-cut basal pneumonia had developed on the right.

On the *sixth day* the abdominal condition continued to improve; 1552 calories of food were taken by bowel and 85 calories by mouth. The abdominal incision was sloughing at its lower angle. Consolidation of the right base persisted and the patient was delirious at times.

On the *seventh day* the abdomen was distended and there was considerable vomiting. Rectal nourishment was discontinued and 1126 calories were given by mouth; all of this nourishment, however, was not retained. The infection of the abdominal incision did not seem to be spreading, but one silkworm-gut suture had torn out. The patient continued delirious at times.

On the *eighth day* the abdomen was softer and the patient was more comfortable. The total vomitus measured 10 ounces, while 5 pints of water and 826 calories of food were retained. The incision showed no marked change. Although the patient was still slightly delirious at times, he was less restless and the area of pulmonary consolidation seemed to be resolving.

On the *ninth day* the abdomen was soft and an alum enema was effectual. The patient retained practically all of 1159 calories of food, only slight vomiting occurring. The abdominal incision was beginning to granulate at the infected area. The mental condition was more rational and the consolidated area in the lung was becoming replaced by moist rales. Coughing was severe, and a note was made that the patient seemed to be on the verge of his crisis.

Unfortunately, toward evening, after a severe coughing spell, the patient became more restless and complained of pain in his incision. On removal of the binder and dressings it was found that about 2 feet of intestine were lying on the surface of the abdomen, the lower angle of the incision having given away. The intestinal coils were replaced under heavy doses of morphin and a few whiffs of

chloroform, and the gaping part of the incision was sutured with through-and-through silkworm-gut sutures over a large gauze sponge, one end of which was allowed to protrude from the lower angle of the incision. Eight hours later the patient died.

It was impossible to obtain permission for an autopsy, but exploration of the abdomen through the operative incision showed that there was no active peritonitis. The sutures obliterating the orifice of the hernial sac were beginning to be absorbed, but very little agglutination of the approximated serous surfaces had occurred, so whether the end result would have been a complete closure of this opening it is impossible to say.

We mentioned in the description of the operation that the free margin of the hernial orifice contained no important structures and that it was incised for about 1 cm. in order to relieve the strangulation. More careful examination, postmortem, however, showed that the inferior mesenteric vein ran less than 2.5 cm. from the free margin, and that only a little further distant was the left colic artery, either of which might have been wounded had the incision been carried farther.

Examination of the intestines showed what wonderful attempts nature makes to restore a damaged organ to normal. Much of the gut had regained its normal color, while those spots which we described as gangrenous had doubled up on themselves and their healthy edges had become adherent, thereby inverting the damaged area more perfectly than the surgeon himself could have done. This occurred in two instances, while a third threatening perforation was protected by adherent omentum.

THE MINERAL METABOLISM OF EXPERIMENTAL SCURVY OF THE GUINEA-PIG.

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and

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I. Historical. A glance at the literature of scurvy since our publication[1] early in 1912 shows the great interest manifested by many in the so-called deficiency diseases. Theodor Fröhlich and Valentine Fürst,[2 3 4] in 1912, reported further studies upon

[1] L. Baumann and C. P. Howard: Arch. Int. Med., 1912, ix, 665.
[2] Ztschr. f. Hyg. u. Infectionskrankh., 1912, lxxii, 1.
[3] Ibid., p. 72.
[4] Ibid., p. 155.

experimental scurvy in a series of 96 guinea-pigs. The disease could be produced with almost mathematical certainty when guinea-pigs were fed on an exclusive diet of oats or other grains. In the course of twenty-eight to thirty days the animals failed and died. Postmortem there was found loosening of the back teeth, hyperemia of the gums, and, microscopically, hemorrhages into the muscles about the joints of the extremities, extravasations about the costo-chondral joints, and frequently epiphysolitis about the upper end of the tibia. Further, the histological changes in the epiphyses and in the bone marrow were identical with those seen in infantile scurvy. They saw similar changes in dogs fed on oatmeal and beef fat and in hogs fed with rye bread, to which boiled beef and rice and dry boiled fish were sometimes added.

Feeding with cabbage, carrots, or dandelions exclusively do not produce such changes, though there may be considerable loss of weight, so that they believe inanition is not the cause of the symptom-complex. Further, they found that various vegetables prevent the development of scurvy or influence its course if present. Boiling or prolonged drying of these vegetables reduces or destroys the antiscorbutic effect. Scurvy-producing foods can be changed to antiscorbutic foods by allowing them to sprout.

They believe that the absence of one or more unknown substances is responsible for the disease and that there is a series of antiscorbutic substances with various properties, but with a common nucleus, which is the true antiscorbutic agent.

They failed to produce scurvy in guinea-pigs by feeding with heated milk unless it were heated to a higher temperature than that used in infant feeding. They could offer no explanation for this difference in the reaction to milk, while the child and guinea-pig react identically to cereals. However, while milk heated to 100° C. does not produce scurvy it does lose its antiscorbutic property. In their last contribution[5] on the preservation and extraction of the specific substance of antiscorbutic foods they point out that dandelion leaves and carrots when dried at 37° C. lose to a marked extent or entirely their antiscorbutic properties. Cabbage juice, which prevents the disease, when heated to 60° to 70° C. has no antiscorbutic effect. The antiscorbutic substances in lime juice and lemon juice are thermostable and the alkaline extract of cabbage and dandelion become almost thermostable when acidified. Hot alcohol (80 per cent.) containing citric acid (1 per cent.) can extract and bring into solution the antiscorbutic substances of freshly dried cabbage. Concerning the exact nature of this substance they are not yet able to speak. It may be of the nature of an enzyme on account of the small amount necessary to prevent scurvy and its thermolability.

[5] A. Holst u. T. Frölich: Ibid., 1913, lxxv, 334.

This experimental production of scurvy by the Scandinavian writers has been confirmed by many, including Kohlbrugge,[6] Hart, Talbot, etc.

Carl Hart[7] produced characteristic bone changes in guinea-pigs when fed on milk alone. The degeneration of the lymphoid marrow into a less vascular, mucoid, or fibrous tissue, together with an impoverization of the osseous tissue at the epidiaphyseal region of the long bones and the persistence of the preparatory calcifying zone with infraction and fractures are the phenomena noted.

Talbot, Dodd, and Peterson[8] emphasized the value in the roentgenogram of the definite "white line" of Fraenkel[9] at the junction of the epiphysis with the diaphysis, which occurs before the subperiosteal hemorrhages and other cardinal symptoms are evident. They confirmed Holst in the production of scurvy in guinea-pigs, in one of which a definite white line could be seen.

F. Lust and L. Klocmann[10] have studied the metabolism in a case of infantile scurvy and found at the height of the disease a slightly abnormal calcium retention. After a month's treatment there was a marked calcium loss, while during the period of convalescence a calcium equilibrium had almost been established. This is in decided contrast to rickets. They conclude there is no evidence that a lack of minerals is a primary or secondary factor in the etiology of the disease.

Schmorl[11] produced in dogs by means of a phosphorus-poor diet a disease that showed great likeness to Barlow's disease but which could not be identified with it. Thus, one animal passed bloody stools, developed convulsions, and died one month after the diet was instituted; another showed difficulty in walking and died in two months. Postmortem there were no hemorrhages and the teeth were normal. The bones of the thorax and extremities showed porosity of the compact layer and diminution of the spongiosa at the epiphyseal ends. The lymphoid marrow was usually replaced by fibrous tissue, with a few spindle and typical marrow cells, a picture resembling that seen in Barlow's disease, except for the infrequency of the hemorrhages. Further, the cartilage proliferation zone was broadened and the calcification zone defective; there were no subperiosteal hemorrhages. The small amount of osseous tissue is due to the diminished function of the osteoblasts and the increased bone destruction. The cartilage itself is not affected but the conversion of cartilage into bone is delayed.

[6] Centralbl. f. Bakteriol., 1911, lx, 223.

[7] Jahrb. f. Kinderheilk., 1912, lxxxvi, 507; Der Skorbut der kleinen Kinder., Stuttgart, 1913.

[8] Boston Med. and Surg. Jour., 1913, clxix, 232.

[9] Fortschr. a. d. Geb. d. Rontgenstrählen, 1903–1904, vii, 231 and 291; 1906–1907, x, 1; 1908, xviii, supplement.

[10] Jahrb. f. Kinderheilk., 1912, lxxv, 663.

[11] Arch. f. exper. Path. u. Pharmakol., 1913, lxxxiii, 313.

Schmorl's work was confirmed by M. Masslow,[12] who described the microscopic changes in the bones in almost identical language, and noted the absence of hemorrhages; he also demonstrated a marked phosphorus deficiency in the bones and all the viscera in his laboratory animals. Masslow concludes, "That in the pathogenesis of disturbances of the osseous system phosphorus plays a distinct role."

Bahrt and Edelstein[13] found postmortem a decrease of ash in the bones especially of calcium and phosphorus very much as in rickets; there was also an increase of the water content of the bones and a diminished calcium content of the muscles.

Morgen and Beger[14] found that rabbits fed on oats alone lost weight and appetite. While an addition to the oats of dicalcium phosphate or sodium chloride had no effect, calcium carbonate caused an arrest of the loss of weight, and the animals did not loose their appetite, but nevertheless they finally died, often with evidence of paralysis. At autopsy there was no pathological change found in the bones or in the alimentary canal, but a marked emaciation and an anemia. The addition of sodium bicarbonate to the diet prevented the loss of weight or caused an immediate rise in the weight of the animal previously fed on oats alone; further, they remained in good health and appetite. The authors believe, therefore, that the cause of the deleterious action of the restricted oats diet is not calcium deficiency but an acid poisoning, as the basic mineral matter of the oats is not sufficient to neutralize the acids which arise during the oxidation of the proteins, namely, phosphoric and sulphuric acids.

Scherer[15] observed in southwest Africa that scurvy prevails when there is a deficiency in the calcium content and an increased alkalinity of the drinking water. He believes that a balance normally exists between the alkalies, potassium and sodium, and the alkaline earths, calcium and magnesium, and that this is disturbed when scurvy appears.

Alex Ingier[16] reproduced scurvy both in the fetus and in the mother guinea-pig by a diet restricted to oats and water. The scorbutic changes in the skeleton were greatest in the earlier embryonic stage. The mother showed signs of the disease at an early period and was more severely affected than a non-pregnant animal. The pathological picture produced resembled that seen in Barlow's disease, by the diminished or even absent bone formation, by the existence of hemorrhages in the bone marrow; by the formation of the structural marrow (gerüst-mark), and by the occurrence of

[12] Biochem. Ztschr., 1914, lxiv, 106.
[13] Ztschr. f. Kinderheilk., 1913, ix, 415.
[14] Ztschr. f. physiol. Chemie, 1915, xciv, 324.
[15] München. med. Wchnschr., 1914, lxi, 1282.
[16] Jour. Exper. Med., 1915, xxi, 525.

fractures. Ingier admits that no experiment has so far succeeded in a direct demonstration of the possible lacking substance in the scorbutic diet.

A. F. Hess and M. Fish[17] found a slightly diminished clotting power of the blood plasma in infantile scurvy, but this defect was not due to a calcium insufficiency. They reported several cases of scurvy which developed in infants fed on milk which was pasteurized by heating to 145° F. for thirty minutes; they were cured by raw milk or fruit juices. Orange juice was found not to loose its efficiency by boiling for ten minutes. The juice of the orange-peel was found as efficacious as that of the fruit itself. They also found that potato was an excellent antiscorbutic and may be added to pasteurized milk instead of barley-water. In a later paper A. F. Hess[18] pointed out that several important symptoms of scurvy have not received the attention they merit. Thus, enlargement of the heart and especially of the right ventricle could be demonstrated by percussion and the roentgenogram. Edema is also a constant symptom in the upper eyelids and over the long bones. Lastly, the nerves may be involved, as shown by increased knee-kicks, superficial tenderness of the limbs, and neurocdema of the optic disks.

Scurvy has been produced in the monkey by Hart and Talbott, but will be referred to at length in a subsequent paper.

A review of the literature of this subject would not be complete without a brief mention of some recent work on beriberi, which is also one of the so-called "deficieney diseases."

In 1912 Susuki, Shimamura, and Odake[19] succeeded in isolating from rice-bran a crystalline picrate from which nicotinic acid and a carbohydrate were obtained. These two bodies are probably inactive; the active substance they had, so far, not isolated, but for it they suggested the name "oryzanin."

Casimir Funk[20 21 22 23] classifies under the term "deficiency diseases" beriberi, polyneuritis in birds, epidemic dropsy, scurvy, experimental scurvy in animals, infantile scurvy, ship-beriberi, and pellagra. He showed that the various curative extracts are essentially phosphorus-free, and therefore the phosphorus theory of Schaumann is still further shattered. He found that the curative substance was present in small amounts in rice (about 0.1 gram per kilogram). He believed it to be an organic base, to which he has given the name "vitamine." This, like uracil and thymine, belongs to the pyrimidine group, and is probably a constituent of nucleic acid.

[17] Amer. Jour. Dis. Child., 1914, viii, 385.
[18] Jour. Am. Med. Assn. 1915, lxv, 1003.
[19] Biochem. Ztschr., 1912, xliii, 89.
[20] Jour. Physiol., 1911, xliii, 395; 1912, xliv, 50; 1912, xlv, 75.
[21] Jour. State Med., 1912, xx, 341.
[22] München. med. Wchnschr., 1913, lx, 2614.
[23] Die Vitamine, Wiesbaden, 1914.

Animals whose food shows a deficiency in this substance loose weight to an enormous extent and cannot be maintained in nitrogen-equilibrium, not even with nitrogen and caloric-rich food. He further believes that scurvy, Barlow's disease, and probably also pellagra and rickets, arise from an absence from the food of this vitamine, and suggests for the group the name "avitaminoses."

Schaumann[24] later confirmed Funk's work on the phosphorus-free nature of the crystalline substance isolated from rice-bran. He, however, believes that this body plays but an intermediate role in the cure of the disease, and that since relatively small amounts are sufficient to cure, and since the effect is also quite persistent, he believes that this activator is of the nature of an enzyme.

Much has been written about the deficiency diseases in the past twelve months, and all are agreed about the close affinity of rickets, infantile scurvy, scurvy, experimental scurvy of the guinea-pig, ship-beriberi, beriberi, polyneuritis gallinarum, and possibly pellagra. Thus, Darling[25] and Brown[26] have both emphasized the close similarity between scurvy and beriberi, clinically, etiologically, and pathologically. Brown writes: "The relation between scurvy, rickets, tetany, and beriberi is intimate and apparently depends upon the balance of the various salts of the body, particularly sodium and potassium on the one hand, and calcium and magnesium on the other, while the position of phosphorus is more variable, although the majority of observers place it along with calcium and magnesium." Excessive retention of sodium and potassium over calcium and magnesium may produce tetany and always rickets.

II. Experimental Scurvy of the Guinea-pig. We first decided to confirm for ourselves the production of experimental scurvy in the guinea-pig. Full-grown healthy young animals were taken and after becoming accustomed to their confinement in a metabolism cage they were found to be in good health and holding their weight. They were then placed on a diet consisting of oats and water. Two series, the first consisting of six and the second of two guinea-pigs, were studied. These animals all gradually lost their appetite, became listless, and walked with difficulty, emaciated considerably, and just before death (which occurred in from twenty-eight to thirty days) developed bloody diarrhea and sometimes hematuria. They were promptly autopsied, and gross and microscopic changes of scurvy found in all the animals. Illustrative protocols follow:

Experiment I. Guinea-pig No. 5, weighed at beginning of experiment (June 28) 616 grams and at day of death (July 27) 266 grams, a loss of 350 grams, or 57 per cent. of body weight. Macroscopi-

[24] Arch. f. Schiff. u. trop. Hyg., 1913, xvi, 350.
[25] Jour. Am. Med. Assn., 1914, lxiii, 1290.
[26] Arch. Pediat., 1915, xxxii, 74.

cally, there was slight looseness of the teeth, but no sponginess of the gums and no intramuscular or serous hemorrhages were found. Microscopic changes were noted as follows: In the femur a section was cut through the head transversely. The blood spaces are seen to be discreet and uncrowded. There is no subperiosteal hemorrhage. The bony trabeculæ stain lightly with hematoxylin. The section through the head shows no change from normal controls. A longitudinal section was cut through the condyles of the femur. There is slight subperiosteal hemorrhage all along the portion proximal to the epiphyseal line. This line is distinguished by the evidence of increased calcium deposit along its proximal border, as shown by the intensity with which the trabeculæ here take the alum-hematoxylin stain. This reaction is most dense in immediate relation to the line, but is continued along the shaft for 1 or 2 mm. The epiphyseal line also marks a distinct difference in blood distribution. On the distal side the blood spaces are discreet and uncrowded. On the proximal side of the epiphyseal line, and extending up the shaft for 2 or 3 mms. the blood spaces are overcrowded and frequently confluent, allowing pools of blood to form. No distinction in the types of cells seen on the two sides of the line could be determined. A section through the head of the tibia showed the identical changes above described. A section through the costochondral junction was studied. Here a slight subperiosteal hemorrhage was noted, and in the bony tissue an overcrowding of the blood spaces with apparent breaking down of the bony partitions separating the same. No unusual degree of calcification was noted. The kidneys were found not to be congested. The epithelium and the glomeruli are intact and there is no interstitial deposit. The spleen shows no congestion, no increase in size or interstitial change, and no increase of red-cell content. The liver is not congested and there is no degeneration of the parenchyma or fatty change in any part. The heart muscle shows its striation well, and there are no granulations or vacuolization of the nuclei. There are no fatty changes in the muscle fibers and no interstitial deposit.

Summary of Microscopic Examination. Viscera nagative. Subperiosteal hemorrhages in the vicinity of the epiphyses of the long bones and at the costochondral junctions. Hemorrhages into the bone substance proximal to the epiphyseal line of the long bones and in the bony part of the ribs adjacent to the cartilage of the same. A reaction in the trabeculæ of the long bones just proximal to the epiphyseal line and most marked in immediate proximity to the line, indicating that the trabeculæ here have a deposit of lime-salts markedly in excess of that on the distal side of the epiphysis or in the shaft of the bone.

Experiment II. September 15, two guinea-pigs from the same litter, three months old, were placed in a metabolism cage and given oats and water *ad libitum*. The urine and feces were not collected.

Guinea-pig No. 1. Large, white male; weight (September 15) 836.51 grams; September 26, 768.00 grams. October 6, it was noticed that the pig was eating little if any; it was very quiet and its fur appeared ruffled. October 9, it weighed 623 grams, a loss of 25 per cent. of body weight. October 11, (the twenty-seventh day) it was so weak that it was chloroformed, and a roentgen-ray picture revealed at the lower epiphyseal line of the left humerus a wide, dense, white line. The autopsy, two hours postmortem, showed slight looseness of the teeth but no swelling of the gums or hemorrhage into the mucous membrane of the mouth or around the hairs of the snout. In the muscles of the biceps and the pectoralis major of the left foreleg a large hemorrhage, 1 cm. in diameter, was found; but none elsewhere; the peritoneal cavity appeared normal. The intestines were strikingly pale as compared with those of guinea-pig No. 2; the liver and spleen appeared normal; the bladder was dilated with urine and revealed a few hemorrhages into the mucosa. On opening the stomach a few petechial hemorrhages were also found in the mucosa. On opening the thorax the lungs were found to be markedly enlarged, particularly in the dependent portions. The four extremities were carefully dissected, particular attention being paid to the condition of the muscles around the joint cavities; no hemorrhages or evidences of disease could be found, except perhaps a little fragility of the bones, but this was hard to estimate. Specimens were removed from all the organs and preserved in 10 per cent. formalin.

Guinea-pig No. 2. A large brown male, weighing 811.02 grams September 15; placed on the same oats and water diet; September 26, it weighed 734.7 grams and October 9, 578.5 grams, a loss of 22 per cent. of body weight. It too began to fail and lose appetite October 6. A roentgen-ray plate was taken October 11, which also revealed a little increase in density of the shadow at the lower epiphyseal line of the left humerus. It died under the anesthetic and an autopsy was performed two hours later. It then weighed 541 grams. Autopsy: Gums appeared relatively bluish, though no visible swelling, no ecchymosis except between the two lower teeth, where the gums appeared a trifle hemorrhagic. The teeth were lusterless, and were easily moved with a light pair of forceps, though not loose enough to be readily extracted; there was a hemorrhage into the muscles on the thoracic surface of the left side. This was about the size of a pea. In the same region on the right a small hemorrhage was seen. No other intramuscular hemorrhage could be found. Upon opening the abdomen the small intestines appeared deeply congested, and there were fair quantities of blood which oozed from the lumen when incised. On the anterior surface of the left lobe of the liver was a large, irregular, yellowish-white area, the size of a nickel, which was removed for examination. The bladder was distended with urine and contained numerous areas of ecchy-

mosis similar to those in guinea-pig No. 1, but more extensive. The thoracic cavity was free from blood, but the lungs appeared large and distinctly hemorrhagic. Sections were made from all the organs. The four extremities were carefully dissected, particular attention being paid to the periarticular tissues; no evidence of hemorrhage could be found. The joint cavities appeared normal. One of the long bones broke with very slight traumatism. All specimens were preserved in 10 per cent. formalin solution.

Microscopic changes were noted as follows: In guinea-pig No. 1 the humerus shows no subperiosteal hemorrhage. The red corpuscles seem more numerous and more generally distributed on the distal side of the epiphyseal line. The line is dense and the deposit of lime-salts is slightly in excess on the diaphyseal side.

The ulna shows no subperiosteal hemorrhage and no changes in the blood distribution. There is at no point any excess of calcification.

The femur was cut through its condyle. There is no subperiosteal hemorrhage. The blood seems in excess on the distal side of the epiphyseal line. The line itself is dense and the trabeculæ of the diaphysis are more infiltrated with lime-salts than those of the epiphysis.

The tibia shows a very slight subperiosteal hemorrhage. The distribution of blood is uneven, though none of the spaces are crowded. The epiphyseal line is dense and the calcification of the trabeculæ of the diaphysis is more marked than that of the epiphysis.

In none of the bones examined was any change in the cellular elements of the marrow noticed.

The lung is slightly congested, but there is no infiltration.

The heart muscle has lost its striation, but the nuclei are not swollen or vesiculated.

The kidney shows a marked degree of postmortem autolysis.

In Guinea-pig No. 2, the sections through the head of the humerus show well-marked subperiosteal hemorrhage. The marrow spaces seem more numerous in the diaphysis and the erythrocytes appear more numerous than normal. The epiphyseal line is well marked and the trabeculæ of the diaphysis are more deeply stained with hematoxylin than those of the epiphysis. The cellular constituents of the marrow are red blood cells and myelocytes, which are granular and stain some with basic and some with acid dyes. There are also quite a number of multinucleated cells. All these elements are evenly disturbed on both sides of the epiphyseal line.

A section through the lower end of the humerus shows a subperiosteal hemorrhage. The epiphyseal line does not appear in the section.

A longitudinal section through the condyles of the femur shows no subperiosteal hemorrhage. There is a very slight diaphysis.

There is no apparent difference in the marrow spaces on either side of the line. The cellular constituents are as above described and evenly distributed.

A section through the shaft of the femur in a longitudinal direction shows no subperiosteal hemorrhage and no excessive calcification. The head of the tibia shows no subperiosteal hemorrhage, but the blood spaces of the diaphysis seem crowded and in some places coalesced. There is a well-marked epiphyseal line showing increased calcium salts, which are also apparent in the trabeculæ of the diaphysis. The cellular constituents are of the same character and distribution as was described in connection with the humerus.

The kidney shows a moderate degree of congestion and the cells are in a state of degeneration in the granular stage. The lungs are congested but not infiltrated.

Unfortunately, in view of a recent publication by Hess,[27] sufficient attention was not paid to the condition of the heart. Hess found in infantile scurvy a tendency to dilatation of the heart, and more especially of the right ventricle.

From these two experiments we felt satisfied that we could reproduce scurvy in the guinea-pig and that the pathological changes noted by Holst and Frölich occurred in our animals.

III. Mineral Metabolism of Normal Guinea-pig. The next point was to determine the normal metabolism of the guinea-pig, as we could find almost nothing in the literature on this subject, and letters of inquiry to various chemists in agricultural colleges, such as H. Grindley, of Illinois, and E. V. McCollum, of Wisconsin, were answered in the negative.

Lukjanow[28] gives the respiratory metabolism but nothing further.

Alezias[29] described the physical characters of the urine and gave the daily average output per 100 grams of body weight, of urea (0.10 grams), of the phosphates (0.003 gram), and of chlorine (0.07 gram). Hunter[30] found that the total nitrogen varied between 1.1 to 3.3 grams pro diem in the normal guinea-pig.

A metabolism cage made by the August Maag Company, of Baltimore, was used. In it was placed a healthy young guinea-pig of 692 grams. The urine was collected in a bottle containing dilute acetic acid and toluol. At the end of twenty-four hours the urine was placed in a glass-stoppered bottle in the ice-box. The feces were carefully picked out of the cage and placed in a wide-mouthed, glass-stoppered bottle until the end of the period, when they were dried to constant weight *in vacuo*, ground to fine powder and put away in a sealed bottle until analyzed. The cages were washed down with distilled water and the washings added to the urine after

[27] Loc. cit.
[28] Ztschr. f. physiol. Chem., 1884, viii, 313.
[29] Compt. rend. Soc. de biol., 1896, xlviii, 213; 1897, xlix, 413.
[30] Jour. Biol. Chem., 1914, xviii, 387.

the latter had been measured. The food, which consisted of oats, white turnips, or white cabbage, was carefully weighed. In Experiment III the food was not analyzed directly but the various mineral constituents were estimated from Koenig's valuable tables. Unfortunately, in the first two periods the guinea-pig lost weight, but was not apparently ill; in the last three periods it gained in weight slightly. Five periods of from five to nine days each were studied in the first experiment and gave the following figures, the first, as far as we know, on the nitrogen and mineral metabolism of this animal. (See Table I.) These figures differ a little from the normal period of Experiments VIII and IX, but a different diet was used.

TABLE I.—NORMAL OUTPUT PER GUINEA-PIG PER DAY. EXPERIMENT 2.

	Nitrogen.		Sulphur.		Chlorine.		Phosphorus.		Sodium.	
	Urine.	Feces.	Urine.	Feces.	Urine.	Feces.	Urine.	Feces.	Urine.	Feces.
Maximum	0.1761	0.0368	0.0394	0.0082	Only one period		0.0099	0.0060	0.0147	0.0082
Minimum	0.1628	0.0228	0.0220	0.0064			0.0076	0.0042	0.0116	0.0035
Average	0.1712	0.0239	0.0329	0.0072	0.0092	0.0010	0.0087	0.0051	0.0131	0.0058

	Potassium.		Calcium.		Magnesium.		Diet.
	Urine.	Feces.	Urine.	Feces.	Urine.	Feces.	
Maximum	0.1260	0.0136	0.0091	Only one period	0.0056	Only one period	Oats and white turnips or white cabbage.
Minimum	0.0962	0.0064	0.0049		0.0048		
Average	0.1111	0.0100	0.0070	0.0021	0.0052	0.0013	

IV. MINERAL METABOLISM OF SCURVY IN THE GUINEA-PIG. Having developed our technic and overcome many small difficulties too numerous to mention, we started two more series, two young guinea-pigs in each series, and ran them for longer periods (fourteen days) on a normal weighed and analyzed diet of carrots, oats, and water until such time as they had been gaining in weight and were accustomed to the laboratory environment. They were then placed on the restricted oats diet and the urine and feces collected in fourteen-day periods. All four animals developed typical symptoms and died but in a rather shorter period than in our former series, namely, in from eighteen to twenty-two days.

Experiment VIII. December 1, 1913, at midday, two young male guinea-pigs from the same litter were placed in a metabolism cage and given a carefully weighed diet of fresh carrots, oats, and water. At the beginning of the period their combined weight was 985 grams. At the end of fourteen days their combined weight was 984.8 grams, showing that they were holding their own. At the end of this normal period, namely, December 15, 1913, the carrots were withdrawn and they received only oats and water. December 17, the urine and feces were discarded and the second or scurvy period started. By the end of the period, after sixteen days of the restricted feeding, both animals were evidently ill, with ruffled coat, loss of appetite, and bodily inactivity; one passed soft and tarry

feces. They now weighed 664.9 grams, having lost 319.9 grams in sixteen days. Period III was now started on December 31, but at 5 P.M., January 2, 1914, or after nineteen days on the restricted diet, one guinea-pig died (No. 1). January 3, 1914, the urine of the second animal was noted to be bloody, and it died January 5, or after twenty-two days on the restricted diet.

Postmortem their combined weight was 544.3 grams, or a loss of 45 per cent. body weight. In both animals the gums were swollen and bluish, but revealed no hemorrhages. The teeth were loose and readily extracted. There were no hemorrhages found in the muscles or into the various serous cavities. The condition of the heart was not noted. The large intestine contained dark fluid material, probably altered blood.

Histology.[31] Sections were made from the upper and lower end of the humerus and the condyles of the femora and the head of the tibiæ. Careful study of these showed slight but definite changes, as in Experiment I, namely, subperiosteal hemorrhages, with extravasation of blood into the intertrabecular spaces of the epiphysis and alterations in the bone marrow. There was some thickening of the epiphyseal line but no evidence of increased deposit of lime-salts. The heart muscle presented poor striation but no nuclear changes.

Experiment IX. December 1, 1913, two young males from the same litter were placed in a metabolism cage and given a carefully weighed diet of fresh carrots, oats, and water. At the beginning of the normal period their combined weight was 990.5 grams; at the end of fourteen days it was 1077.7 grams; in other words, these animals gained 87.2 grams under similar conditions as those of Experiment VIII. They ate voraciously and were possibly younger animals which had not reached their full growth at the beginning of the experiment.

December 15, the carrots were withdrawn from the dietary. December 17, the second period was begun. December 31, the end of the second period (*i. e.*, after sixteen days on the restricted diet) both animals showed a ruffled coat, loss of appetite, and bodily inactivity, while both were passing dark, loose stools. They now weighed 733.3 pounds, having lost 344.4 grams. Period III was now started January 2, 1914. One guinea-pig died eighteen days after the onset of the oats diet. January 3, the other animal passed bloody urine, and on January 5 it died after twenty-one days on the restricted diet.

Postmortem their combined weight was 610.8 grams, or a loss of 56.6 per cent. of body weight. They showed the same blue color to the gums and the teeth were loose. There were no hemorrhages into the gums, muscles, joints, or serous surfaces found. The

[31] For the histological study of our animals we wish to express our thanks to Dr. Royce, the pathologist of the University Hospital.

large intestine was filled with dark, tarry material, probably in great part altered blood.

Histology. Sections were made from the head of the humerus, the head, and the lower end of the radius, the condyles of the femur and the head of the tibia. While subperiosteal hemorrhage was not so frequent, there were constant hemorrhages into the trabeculæ spaces of both epiphyses and diaphyses, with fibrin in considerable amounts distributed in masses in some areas and as a network in others. The epiphyseal line too was usually thickened and stained deeply with hematoxylin. In one animal the lung showed infiltration of the walls of the alveoli with leukocytes, while some of the alveoli were filled with fibrin, red, and white blood cells. The heart was not examined.

From the above protocols it will be seen that we had succeeded in reproducing both gross and microscopic changes in our animals which have been considered as pathognomic of scurvy in the guinea-pig.

Procedure. Profiting by our experience in former experiments the urine was collected under toluol in a flask to which 5 c.c. of dilute acetic acid were added to render the urine acid and to prevent decomposition. It was daily collected and stored in a glass-stoppered vessel and placed in an ice-box. At the end of each period the wire floor, bottom, and sides of the cage were carefully washed down with distilled water and the washwater added to the urine and further diluted to 1500 c.c. Varying amounts of this were taken for analysis and duplicate estimations were made and repeated until they corresponded within the experimental error.

Every two days the feces were carefully picked out with clean forceps and in this way separated from the hulls and oats in the bottom of the cage. They were placed in wide-mouthed glass-stoppered bottles and preserved in the ice-box until the end of the period. They were then dried to constant weight *in vacuo* as described in a former paper, ground in a mill to a fine powder, placed in a glass-stoppered bottle, sealed with paraffin, and examined for the various constituents at our leisure. The nitrogen content of the distillate was, of course, added.

The intake of the various elements was calculated as follows: A large supply of oats and carrots was obtained at the outset of the experiment. The water content of each was determined and the material placed in sealed containers. Weighed portions were placed at the disposal of the animals. The unconsumed food, including the oat-hulls, was then dried to constant weight, powdered and analyzed, and the mineral content in each instance deducted from that found in the oats and carrots which had been placed in the cage.

The first period of fourteen days represents the normal period on a weighed mixed diet for two healthy animals. (See Tables II and III.)

TABLE II.

Period.	No. days.	Weight in grams.	Diet.	Urine in c.c. +washwater	Dried feces.	Total nitrogen. Intake.	Total nitrogen. Output. Urine.	Total nitrogen. Output. Feces.	Total nitrogen. Balance.	Total sulphur. Intake.	Total sulphur. Output. Urine.	Total sulphur. Output. Feces.	Total sulphur. Balance.	Chlorin. Intake.	Chlorin. Output. Urine.	Chlorin. Output. Feces.	Chlorin. Balance.
Experiment 8																	
2 guinea-pigs I	14	At onset =985.0 At end =981.8 loss =0.2	Carrots =94.45 Oats =461.7 Hulls left =20.3	1500 c.c.	73.91	Carrots =1.4575 Oats =10.7920	3.6435	2.5637	6.0423+	Carrots =0.1322 Oats =0.7504	0.4740	0.2300	0.1786+	Carrots =0.1916 Oats =0.4730	0.2612	trace[31]	0.4034+
II	14	At onset =984.8 At end =664.9 Loss=319.9	Carrots =0 Oats =209.0 Hulls left =15.77	1500 c.c.	46.72	Carrots =0 Oats =4.7769	5.9850	1.5582	2.7663−	Oats =0.3286	0.4019	0.1784	0.2517−	Carrots =0 Oats =0.2027	0.2471	trace[31]	0.0444−
Experiment 9																	
2 guinea-pigs I	14	At onset =990.5 At end =1077.7 Gain =87.2	Carrots =176.8 Oats =478.02 Hulls left =27.97	3000 c.c.	81.5	Carrots =2.7320 Oats =11.0640	3.7905	3.1101	6.8951+	Carrots =0.2475 Oats =0.7652	0.5822	0.2659	0.1646+	Carrots =0.3586 Oats =0.4778	0.4082	trace[31]	0.4282+
II	14	At onset =1077.7 At end =733.3 Loss=344.4	Carrots =0 Oats =270.5 Hulls left =33.3	1500 c.c.	59.27	Carrots =0 Oats =5.9619	5.5755	2.4854	2.0990−	Oats =0.4033	0.3607	0.1592	0.1166−	Carrots =0 Oats =0.2401	0.1707	trace[31]	0.0694+

Period.	Total phosphorus. Intake.	Total phosphorus. Output. Urine.	Total phosphorus. Output. Feces.	Total phosphorus. Balance.	Sodium. Intake.	Sodium. Output. Urine.	Sodium. Output. Feces.	Sodium. Balance.	Potassium. Intake.	Potassium. Output. Urine.	Potassium. Output. Feces.	Potassium. Balance.	Calcium. Intake.	Calcium. Output. Urine.	Calcium. Output. Feces.	Calcium. Balance.	Magnesium. Intake.	Magnesium. Output. Urine.	Magnesium. Output. Feces.	Magnesium. Balance.
Experiment 8																				
2 guinea pigs I	Carrots =0.3228 Oats =1.8950	.6158	.9065	.6964+	Carrots =0.9161 Oats =1.0225	1.4163	0.2884	0.5747+	Carrots =1.8420 Oats =2.3590	1.5168	0.5693	2.0849+	Carrots =0.3729 Oats =0.3108	.1170	.1701	.3966+	Carrots =0.1392 Oats =0.3982	.0795	.2218	.2361+
II	Carrots =0 Oats =0.8334	.5339	.5251	.2256−	Carrots =0 Oats =0.5805	0.4792	0.2056	0.1013−	Carrots =0 Oats =0.0239	1.3106	0.3831	0.6998−	Carrots =0 Oats =0.1291	.1704	.1542	.1955−	Carrots =0 Oats =0.1747	.6708	.0841	.0198+
Experiment 9																				
2 guinea pigs I	Carrots =0.6043 Oats =1.9368	.5983	.9991	.9437+	Carrots =1.7150 Oats =1.3734	1.1048	0.3260	1.6576+	Carrots =3.4470 Oats =2.3961	3.8387	0.6139	1.3608+	Carrots =0.6639 Oats =0.3095	.2358	.1793	.5571+	Carrots =0.2475 Oats =0.4063	.1141	.2201	.2896+
II	Carrots =0 Oats =1.0302	6149	.7273	3120−	Carrots =0 Oats =0.6791	0.3562	0.2845	0.0384+	Carrots =0 Oats =1.2103	0.9469	0.4860	0.1926−	Carrots =0 Oats =0.1446	.1080	.1837	.1471−	Carrots =0 Oats =0.2151	.0698	.0948	.0505+

[31] Not weighable.

TABLE III.

Output per Guinea-pig per Day.

	Nitrogen.		Sulphur.		Chlorine.		Phosphorus.	
	Urine.	Feces.	Urine.	Feces.	Urine.	Feces.	Urine.	Feces.
Normal period VIII[1]	0.1301	0.0916	0.0170	0.0082	0.0093	trace	0.0220	0.0324
Normal period IX[1]	0.1353	0.1110	0.0208	0.0095	0.0146	trace	0.0214	0.0357
Average	0.1327	0.1013	0.0189	0.0088	0.0119	trace	0.0217	0.0341
Abnormal period VIII[2]	0.2140	0.0557	0.0143	0.0064	0.0088	trace	0.0190	0.0190
Abnormal period IX[2]	0.1991	0.0888	0.0129	0.0057	0.0061	trace	0.0229	0.0260
Average	0.2065	0.0723	0.0136	0.0061	0.0075	trace	0.0210	0.0239

	Sodium.		Potassium.		Calcium.		Magnesium.	
	Urine.	Feces.	Urine.	Feces.	Urine.	Feces.	Urine.	Feces.
Normal period VIII[1]	0.0506	0.0103	0.0552	0.0203	0.0042	0.0061	0.0028	0.0079
Normal period IX[1]	0.0394	0.0116	0.1371	0.0230	0.0084	0.0064	0.0051	0.0078
Average	0.0450	0.0110	0.0962	0.0217	0.0063	0.0063	0.0039	0.0079
Abnormal period VIII[2]	0.0171	0.0073	0.0466	0.0137	0.0061	0.0055	0.0025	0.0030
Abnormal period IX[2]	0.0127	0.0101	0.0338	0.0174	0.0038	0.0065	0.0025	0.0034
Average	0.0149	0.0087	0.0402	0.0156	0.0050	0.0060	0.0025	0.0032

Intake per Guinea-pig per Day.

	Nitrogen.	Sulphur.	Chlorine.	Phosphorus.	Sodium	Potassium.	Calcium.	Magnesium.
Normal period VIII[1]	0.4374	0.0315	0.0237	0.0792	0.0814	0.1500	0.0244	0.0192
Normal period IX[1]	0.4927	0.0361	0.0299	0.0907	0.1103	0.2087	0.0347	0.0233
Average	0.4650	0.0338	0.0268	0.0850	0.0959	0.1794	0.0296	0.0213
Abnormal period VIII[2]	0.1706	0.0177	0.0072	0.0298	0.0207	0.0365	0.0046	0.0062
Abnormal period IX[2]	0.2129	0.0144	0.0086	0.0368	0.0242	0.0443	0.0051	0.0077
Average	0.1918	0.0131	0.0079	0.0333	0.0225	0.0404	0.0049	0.0070

Average Balance per Guinea-pig per Day.

	Nitrogen.	Sulphur.	Chlorine.	Phosphorus.	Sodium.	Potassium.	Calcium.	Magnesium.
Average intake, normal periods	0.4650	0.0338	0.0268	0.0850	0.0959	0.1794	0.0296	0.0213
Average output, normal periods	0.2340	0.0277	0.0119	0.0558	0.0560	0.1179	0.0126	0.0118
Balance, normal periods	+0.2310	+0.0061	+0.0149	+0.0292	+0.0399	+0.0615	+0.0170	+0.0095
Average intake, abnormal periods	0.1918	0.0131	0.0079	0.0333	0.0225	0.0404	0.0049	0.0070
Average output, abnormal periods	0.2788	0.0197	0.0075	0.0440	0.0236	0.0558	0.0110	0.0057
Balance, abnormal periods	−0.0870	−0.0066	+0.0004	−0.0107	−0.0011	−0.0154	−0.0061	+0.0013

The second period of fourteen days represents the abnormal or scurvy period. It was preceded by a fore-period of two days, the urine and feces of which were discarded.

The third period was unfortunately so short and the animals were eating so little and excreting so little urine and feces that enough material was not obtained for purposes of analysis of all the constituents. These were kept, however, in case there was a striking increase or decrease in the balance of any one mineral, which could be confirmed in this period.

Analytical Method. The methods were similar to those used in Experiment I. Extra precautions were necessary to render the silica present in some of the material insoluble. This was usually accomplished by evaporating the acid ash-extract to dryness on

the water bath, then drying at 110 to 120° for two hours in the drying oven. This precaution was necessary in the estimation of the calcium in the food, urine, and feces.

V. Discussion of Results. The animals employed in these experiments were vigorous but immature. They retained considerable nitrogen and two gained in weight during the normal period. When the diet was restricted to oats an insufficient amount of nitrogen and an inadequate number of calories were consumed, with a consequent loss of nitrogen and body weight. This factor must be borne in mind in the interpretation of the analytical results. It is impossible with the available data to estimate the role which starvation played in these experiments. However, it is well to note that starvation alone will not produce the pathological changes observed, as shown by Holst and Frölich.

Nitrogen, Sulphur, and Phosphorus. The excretion of these elements during the abnormal periods was remarkably high, and this is hardly to be explained by starvation alone. For example, during the first normal period the animals consumed about 12 grams of nitrogen and excreted 3.64 grams in the urine, and 2.56 grams appeared in the feces. In the abnormal period they ingested 4.77 grams, but excreted about 6 grams in the urine and 1.56 grams in the feces. This may indicate increased protein katabolism.

Sodium and Chlorine. During the first abnormal period there was but a slight loss, and during the second a gain in sodium and chlorine. One might assume that sodium chloride did not play an important role in the etiology of this disease, although the bulk of the sodium is evidently not excreted in this form.

Potassium. This element is more abundant in the vegetable diet administered than any of the other bases. Considerable quantities were retained during the normal periods. The loss of this element during the abnormal periods is greater than that of sodium.

Calcium and Magnesium. A considerable part of the calcium is excreted through the urine. The amount excreted during the abnormal periods is notably high. Magnesium is the only element which was consistently retained during the four periods. The loss of calcium during the "oats" period may partly account for the diminished bone formation observed in this disease.

VI. Conclusions. An examination of the evidence, both experimental and clinical, leads to the view that scurvy, and perhaps the allied diseases as well, are due to the absence of certain substances in the dietary. The lack of this material appears to have a profound effect on the mineral metabolism of the guinea-pig.

THE PRINCIPLES AND PRACTICE OF REGISTERING HEART SOUNDS BY DIRECT METHODS.[1]

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AND

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Introduction. A simple method of registering heart sounds in conjunction with other graphic tracings, or the electrocardiogram, is frequently desirable. No means of accomplishing this has proved entirely satisfactory. The most successful procedure hitherto devised for recording sounds is that of Einthoven[2] and his associates.[3] The sound vibrations are transformed by the aid of a microphone and secondary coil into electrical variations which are recorded by the string galvanometer. In order to use this procedure in connection with the electrocardiograph two galvanometers are required, a luxury not enjoyed by most institutions. The direct registration of heart sounds, meaning thereby the transmission of sound vibrations to membranes capable of directly recording these oscillations photographically, seems to be the most expeditious procedure.

The impression may easily be gained, in reading the literary champions of various methods, that this may readily be accomplished by installing their particular form of apparatus. An actual inspection of the published records is sufficient to convince even the uninitiated that the total number of true sound-records obtained in this way is not very great. The sound-records obtained by the phonocardiographic method of Einthoven have set a standard by which the records obtained by direct registration may well be judged. They show (Fig. 1 *A*) that the vibrations start from a horizontal line and oscillate above and below it, that the frequency as well as the amplitude alters from one vibration to another, and that these characteristics vary in different individuals. Most of the published records taken with direct methods show no similarity to these tracings. This is the case of the records published by Bull,[4] Van Zwaluenberg and Agnew,[5] Weiss and Joachim,[6] Gerhartz,[7] and Ohm,[8] photographic reproductions of some of which are shown in Fig.

[1] Received for publication October 7, 1916.

[2] Arch. f. d. gesam. Physiol., 1907, cxvii, 461; 1907, cxx, 31.

[3] Fahr: Heart, 1912, iv, 147. Battaerd: Heart, 1915, vi, 121.

[4] Quart. Jour. Exp. Med., 1911, iv, 289.

[5] Heart, 1912, iii, 343.

[6] Arch. f. d. gesam. Physiol., 1908, cxxiii, 361.

[7] Registrirung des Herzschalls, Berlin, 1911, p. 72.

[8] Ztschr. f. exp. Path. u. Therapie, 1912, xi, 149.

1 *B, C, D*. Records have been taken by direct methods, however, which compare favorably with those of the electrocardiographic curves. Thus, Frank[9] obtained such tracings from dogs by using his segment capsules and Edens,[10] in Fr. Müller's clinic, was able to

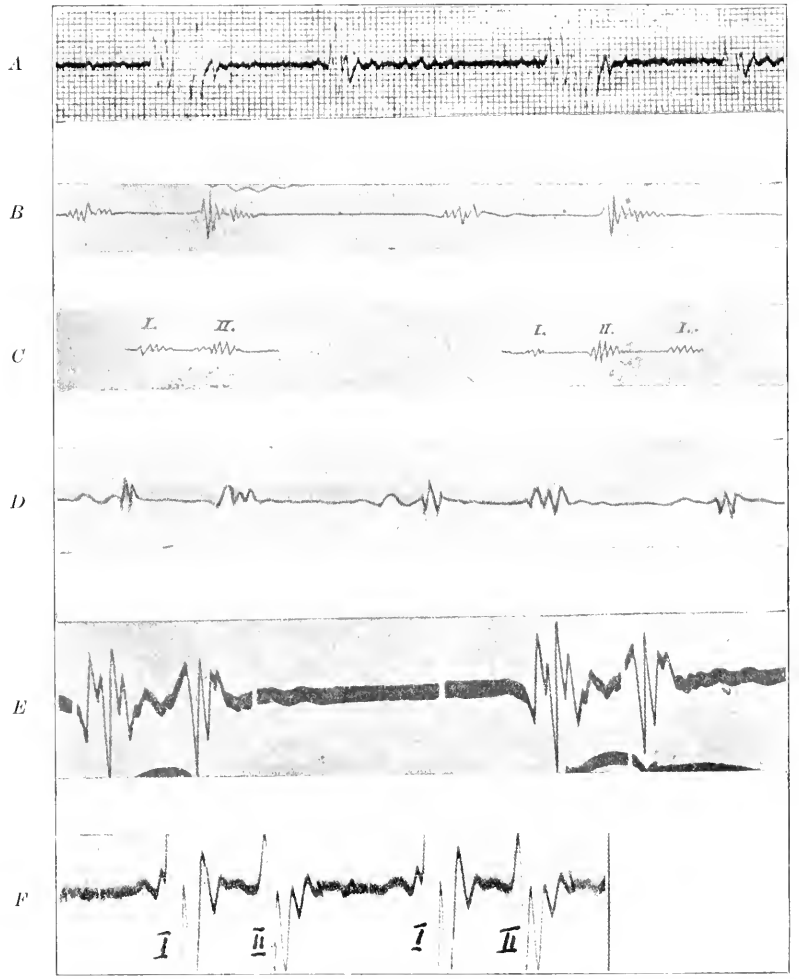

Fig. 1.—Comparison of heart-sound vibrations obtained by Einthoven's microphone method, *A*, compared with records obtained by various direct methods; *B*, curves of Weiss and Joachim; *C*, curves of Gerhartz; *D*, curves of Ohm; *E*, curves of Frank; *F*, curves of Edens.

obtain a few records from selected patients. Photographic copies of these records are also shown in Fig. 1 *E, F*.

[9] Ztschr. f. Biol., 1905, xlvi, 524.
[10] Deutsch. Arch. f. klin. Med., 1910, c, Plate II.

When all is said the fact remains that the direct registration of sounds has been used satisfactorily only in selected cases, and when used by the less experienced in routine clinical work has resulted in repeated disappointment or total failure. We have added no new form of apparatus to the already long list of available instruments,[11] but by applying certain principles in the practice of registering sounds have succeeded in successfully recording true sounds in the average routine cases. As far as the Frank capsules are concerned, experience has taught us that failure to record true sounds is not due to the inadequacy of the apparatus, but success is contingent upon attention to certain technical details and upon a constant comprehension of the fundamental guiding principles upon which their use is based. A consideration of the principles and practice of heart-sound registration by direct methods is therefore of current interest.

The Principles of Direct Sound Registration. All methods of direct sound registration endeavor to copy the principle used by the human ear in auscultation. A funnel or stethoscope bell is snugly applied over a cardiac area and the sounds are led by a rubber tube to a capsule covered by a very light membrane. This membrane may be compared to the tympanic membrane of the ear. The conveyed sounds cause both membranes to vibrate. In the case of the ear the vibrations are transmitted by a series of auditory ossicles to the internal ear and are then transformed to nerve impulses registering in the auditory cortex. In the case of the artificial membrane the vibrations are transformed to oscillating light beams, which are photographed on a moving sensitive film.

The Physics of Vibrating Membranes. Since the vibrating membrane constitutes the chief and fundamental part of every sound-recording mechanism it is important to recall a few physical facts applying to such membranes. Every freely swinging membrane if suddenly set in motion continues to vibrate with gradually diminishing amplitude (Fig. 2 *A*) before coming to rest. Such a membrane is called *periodic* and the vibrations are spoken of as the *inherent* or *free* vibrations. The time consumed by each vibration is called the *inherent vibration period* (often designated by T), while the number of vibrations it would execute in a second is the *vibration frequency* of a membrane (often designated by N). It is obvious that the frequency is the reciprocal of the period $N = \frac{1}{T}$. Hence, we say synonymously that an instrument has a short period or a high frequency. The number of vibrations taking place before complete rest occurs depends on the friction due to damping. If damping is slight, each successive vibration is only slightly diminished in amplitude and a considerable number of free vibrations result (Fig. 2 *A*). On the other hand, if damping is moderately

[11] Wiggers, The Circulation in Health and Disease, Philadelphia, 1915, p. 177.

great, only a few vibrations take place before rest occurs (Fig. 2 *B*). The rate of reduction in amplitude is called the *vibration decrement*. If damping is great enough to prevent all free vibrations the apparatus is called *aperiodic* (Fig. 2 *C*).

Every membrane that has its own tendency to swing may follow imparted vibrations, such as extraneous sounds. It is obvious that no membrane can follow sounds having a frequency greater than

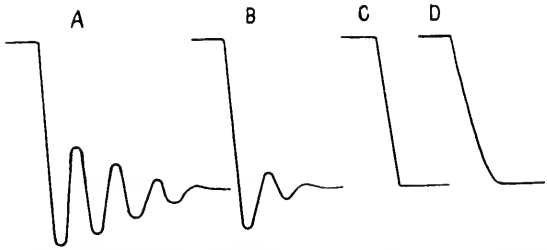

FIG. 2.—Diagrams showing the behavior of a membrane under different damping conditions when a strain is suddenly released. *A*, undamped membrane; *B*, partially damped membrane; *C*, ideally damped membrane; *D*, overdamped membrane.

the inherent period of the instrument. It reacts with maximum vibrations to sounds having the same frequency as the membrane itself, a phenomenon called *resonance*. If a miscellaneous series of waves, equal in amplitude but differing in their periods, are recorded by a membrane whose period is equal to some of these waves, but is greater or less than others, they will not be recorded in equal amplitude. As shown schematically in Fig. 3 the vibrations whose period closely approximates that of the apparatus will appear larger

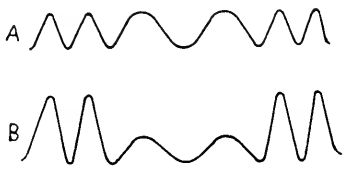

FIG. 3.—Diagram to show the influence of resonance in reproducing sound vibrations. *A*, a theoretical series of vibrations of equal amplitude but varying periods; *B*, record of same by membrane having an inherent period corresponding to the first and last waves.

than those occurring at a rate which is either faster or slower. In recording heart sounds, therefore, it is necessary to employ a membrane whose period is not only as short as but very much less than the shortest oscillation to be recorded.

It is possible for the damping of a membrane to be excessive. When this occurs the membrane is prevented from following the rate of the imparted vibrations accurately; hence, not only is their

contour altered but their amplitude is unduly diminished. On the other hand if a membrane is not aperiodic it has a tendency to add its own vibrations to the imparted vibrations. When it is difficult to produce an optimum damping it is more rational to err slightly toward a periodic system and maintain the apparatus only approximately aperiodic, provided always that the apparatus has an inherent vibration rate well in excess of the oscillations that it records.

Practical Tests to Determine the Efficiency of an Apparatus. An efficient sound-recording system should be so designed that its inherent vibration frequency is not less than 100 and is preferably more than 150 per second; that the decrement of the vibrations is rapid and the sensitiveness of the membrane is so great that 1 mm. of water-presssure in the closed system will deflect the beam of light projected on the camera about 4 cm. By what practical tests can the operator determine whether these conditions are fulfilled?

The vibration frequency may be determined in a number of ways. The method employed by us consists in allowing a periodic membrane which has previously been drawn out of equilibrium to execute its natural vibrations when suddenly released. The simplest means of accomplishing this consists (1) in closing the tube-end commonly connected to the chest receiver; (2) in cautiously creating a slight negative pressure within the system by suction on the side stopcock; (3) in quickly opening the side tube while the paper or film of the photokymograph is running. In this way, as shown in Fig. 5 *E*, a curve is obtained in which each wave decreases by an amount proportionate to its predecessor. Comparison with a simultaneously recoded tuning fork curve enables one to figure the vibration period.

A second method suggested by Van Zwaluenberg and Agnew[12] utilizes the principle of resonance. By singing a scale of notes in an even voice into the mouth-piece a series of vibrations for each note can be recorded photographically. Their amplitude will vary, for the membrane responds with the maximal vibrations to the note having the same frequency as the membrane. The difficulty consists in singing sounds of equal intensity. If the loudness of the singing voice changes the amplitude will necessarily vary in proportion.

The decrement of the inherent vibrations depends on the degree of damping. In the Frank capsules no special mechanism for damping exists, but it is unnecessary, and in fact undesirable, as we have experimentally determined. The damping of the air column is materially affected by the relative side opening. The determination of the decrement of such an open system requires special procedures

[12] Loc. cit.

to draw the membrane out of equilibrium. This cannot be carried out satisfactorily without difficulty. A tiny steel splinter may be centrally supported on the membrane and the membrane deflected by an electromagnet, or a light string may be included in the membrane at the time of its manufacture by which the membrane is drawn out. By suddenly demagnetizing the coil in the first instance, or by quickly severing the string, the membrane is thrown into a few damped oscillations. The relative decrease in succeeding vibrations should be great and not more than two or three vibrations should occur.

As a rule an apparatus may be regarded as approximately aperiodic without this special test when the vibrations of the closed system decrease rapidly in amplitude, as shown in Fig. 5 *E* and *F*.

The sensitiveness of the system may be determined by connecting to the rubber tube of the closed system a U-shaped water manometer in which the pressure can be varied slightly by a piece of closed rubber tubing attached to one limb. The excursion of the beam of light when 1 mm. of water-pressure exists in the closed system may be read on the centimeter scale of the camera.

Some Difficulties Attending the Separation of Sound Waves from Mechanical Impacts. When a stethoscope bell is applied over the apex region two sets of pressure variations are transmitted through the connecting tube to the membrane: the one, a rapid set of compressions and rarefactions caused by sound waves, the other, the mechanical variations caused by the apex beat. The latter are so slow that they make no impression upon the ear during auscultation. The recording capsules are sensitive to both disturbances; consequently, if a closed system is used a composite curve of the cardiogram and the superimposed sounds is recorded (Fig. 5 *A*). To annul the grosser mechanical variations the expedient suggested by Einthoven has generally been applied—of introducing a side opening of sufficient size into the system. This expedient introduces a number of interlinking difficulties in direct sound registration. In the first place a more sensitive membrane is required. A membrane that records all sounds in the composite curve yielded by a closed system fails to record the sounds entirely when the side tube is open or, when closure is not sufficient, *registers a number of mechanical variations that may readily be misinterpreted as diminutive sound waves*. This is illustrated in Fig. 5 *B*. These vibrations are due to the fact, shown in the apex curve of Fig. 4 *A*, that at the time of the two heart sounds the variations of the apex beat are peculiarly abrupt and rapid, and hence readily affect less sensitive capsules even when a side leak is introduced. If the apparatus is periodic and its frequency low the impact may inaugurate a series of inherent after-vibrations which, *because they occur at the time when the sounds may be expected to come*, are easily mis-

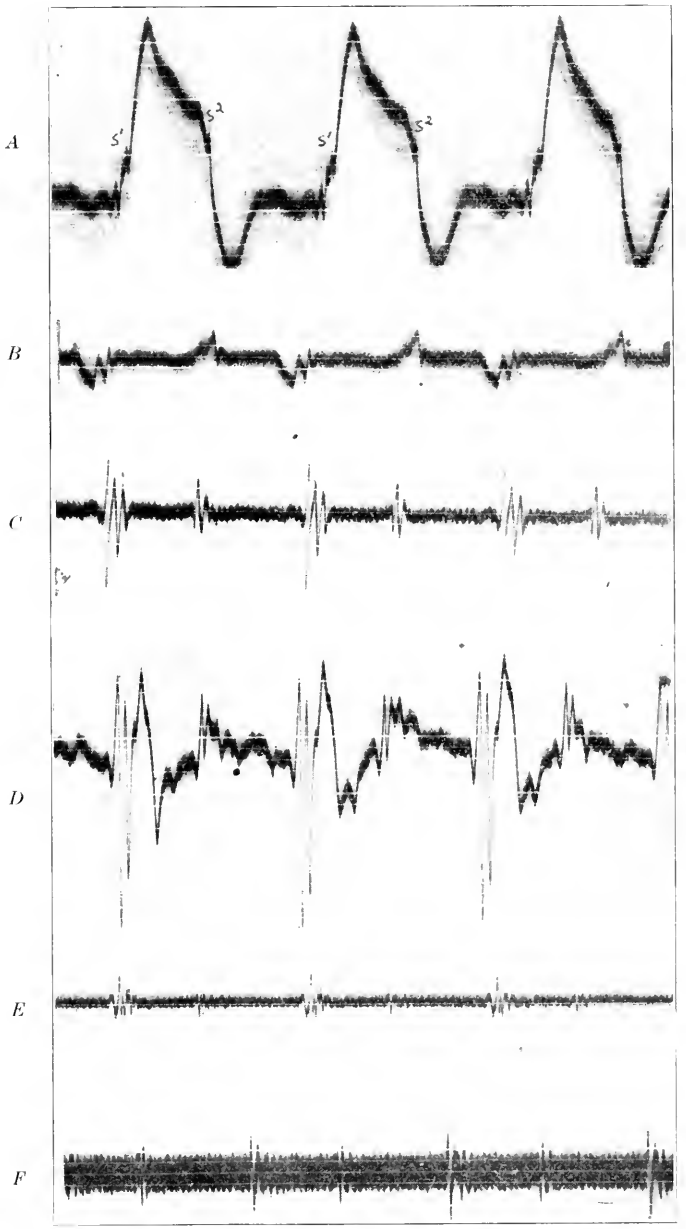

FIG. 4.—Series of records from one individual, illustrating the principles and practice of sound registration. *A*, apex beat with sound vibrations at *S'* and *S''* recorded by a closed system from subject lying on left side; *B*, curve with same apparatus and side tube open. True sound vibrations are absent and remnants of apex curve substituted. These form the basis of pseudo-sounds recorded frequently. *C*, record from same subject by our modified capsules with side tube widely open; *D*, same, with partially closed side opening; *E*, same, with excessive side opening; *F*, same, with wide light band tending to obscure sound vibrations.

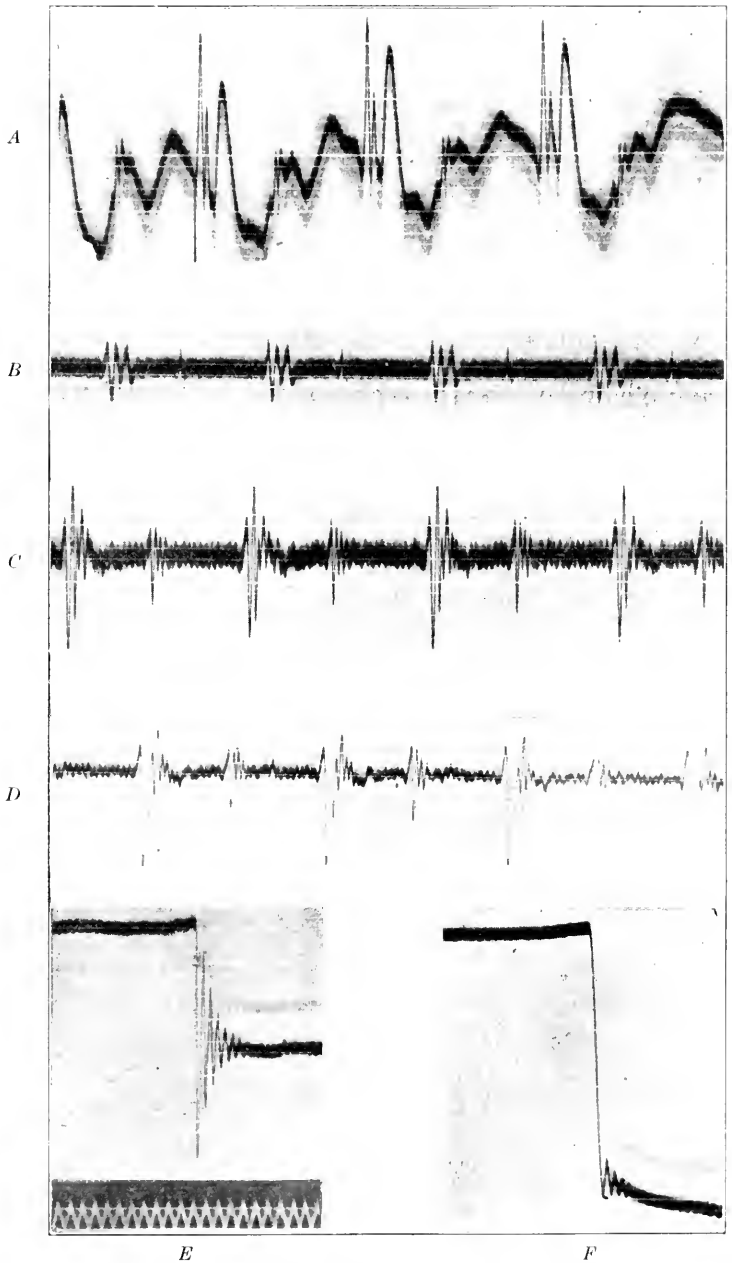

FIG. 5.—*A*, apex curve with same apparatus as used in Fig. 4; *A*, taken with subject in sitting posture; *B*, curve recorded with same apparatus but side tube open; *C*, record from same subject taken by our modified capsules; *D*, more satisfactory record of same due to use of narrower band of light; *E*, curve showing the method of determining the vibration frequency; *F*, curve showing the damping influence of an open side tube.

interpreted as cardiac sounds. This is an error into which many investigators who professed to record sounds by the direct method have been led, as can be seen from a comparison of our spurious sound records in Figs. 4 *B* and 5 *B* with those of Fig. 1 *B*, *C*, *D*. It should be distinctly emphasized that the presence of a depression or series of waves at the time when the two sounds may be expected to occur is in itself not a guarantee that they are due to sound vibrations.

This difficulty may be overcome by employing a more sensitive membrane which permits the use of a relatively larger side opening. Curves obtained by such a membrane are shown in Figs. 4 *C* and 5 *C*. Various types of membrane have been suggested, but of all rubber, on account of its stability and elasticity, is probably the best. The thinnest rubber dam commercially available (condom thickness) is too thick to react to sounds from routine clinical cases. By special favor we have succeeded in securing a still thinner variety of rubber dam, but its keeping quality is not good. After considerable experimentation we are able to manufacture our own rubber membrane of a filmy thinness. This is accomplished by drawing the surface of a capsule through a film of rubber cement which has been allowed to thicken somewhat by exposure to the air.

When such a sensitive membrane is employed the difficulty arises that they are responsive to the slightest extraneous noises. The noise of running motors, the hum of fans or tuning-forks, the spoken voice, the walk of the experimenter, the rattle of passing wagons or the gongs of cars are a few of the interfering noises which affect the sensitive membrane, exposed as it is to the air. Furthermore, respiratory sounds, intestinal gurgling, muscular movements of respiration are all liable to be led by the tubing to affect the membrane from the inside. Unlike the human ear, which can be trained to mentally exclude sounds it chooses not to hear, these capsules are not selective but record all vibrations. Although satisfactory means have not been suggested to obviate all these vibrations, very satisfactory records can be obtained by operating the apparatus in a not too quiet room, as shown in Figs. 4 *C* and 5 *C*, *D*. Recently it has become possible to materially reduce in number the accidental-room vibrations. This was accomplished by inclosing the membrane in a housing with a glass window, thus preventing the impingement of accidental room-vibrations (*cf.* February issue of *Am. Jour. of Physiol.*, 1917). These records have one advantage over the phonocardiographic curves of Einthorn, *i. e.*, they do not add adventitious vibrations due to the readjustment of carbon particles in the microphone, such as often causes trouble when even a moderately strong current passes.

It is frequently difficult to determine the optimum side opening. The degree of opening required depends on the sensitiveness of the membrane and on the relative intensity of the sounds and apex

variation. If the opening is insufficient the sound curve is partly deformed by an element of apex curve, as shown in Fig. 4 *D*. If the opening is too large the smaller vibrations may fail to be recorded (Fig. 4 *E*) and occasionally the second sound may be entirely absent. When the second sound is soft and the first accentuated it may be very difficult to obtain a record which does not show some distortion due to the apex curve and still records the second sound satisfactorily. In practice it is therefore usually desirable to record a series of sound tracings with different side openings. The first tracing is taken with the side opening so adjusted that *two sets* of oscillations are clearly visible in the projected band of light. A second and third record are subsequently taken with a greater and less degree of closure respectively. By comparing the three curves all the sound components can be satisfactorily established.

THE APPARATUS AND TECHNIC IN RECORDING HEART SOUNDS. *The Sound-recording System.* In recording heart sounds a communicating system, consisting essentially of a receiver, rubber tubing, and a Frank segment capsule, transforming the sound vibrations into oscillations of a beam of light, is utilized. The receiver found to give the best results is an open one, though not of the type of any of the numerous models of stethoscope bells. It is of brass and 9 cm. in diameter, which is somewhat larger than most of the more popular stethoscope bells. This point is quite important in recording heart sounds, for less perfect results were obtained when receivers built to the same scale but covering smaller areas of chest wall were used. A firm and immovable apposition between the chest wall and the receiver is essential. A very considerable increase in amplitude and clearness of the sounds often occurs when the receiver is merely pressed more firmly to the chest. A simple means of obtaining the desired apposition is afforded by strapping an elastic belt around the chest. This presses the open aspect of the receiver against the chest when the tubular transmitting part is fitted through a hole in the belt fabric.

It is not desirable to record heart sounds through a receiver held away from the chest wall. The sounds heard over different cardiac areas and attributed to the heart in reality are merely vibrations of the chest wall and are therefore best recorded by direct contact. In addition, without direct contact of the receiver, a very delicate registering system must be used which has the drawback that many extraneous vibrations are recorded. The clarity of the sound-records, just as that of the usual stethoscopic auscultation, is diminished by such factors as excessive fat, a large breast, emphysema, etc.

Although an apex beat that corresponds more definitely with the position changes of the heart is obtained when the subject lies on the left side (*cf.* Figs. 4 *A* and 5 *A*), the sounds are recorded more readily in the sitting posture. A comparison of Figs. 4 *C* and 5 *C*.

shows that more vibrations are recorded in the latter posture. This is probably due to the damping of the chest vibrations by the bedding.

The rubber tubing which leads from the receiver is soft and flexible, 5 mm. in diameter and not more than 70 cm. long. It is supported from above at a short distance from the chest by a long, lax, spiral spring, giving to the tube when in motion a very low vibration frequency. The delay in transmission was found to be 0.0027 second, a negligible time interval for ordinary purposes.

The Frank capsule supported upon the miniature cannon carriage, as previously described by one of us,[13] is used as the recording mechanism. There is a difference in that the material composing the membrane is an extremely thin film of rubber prepared as follows: A glass tube is withdrawn from a jar of rubber cement and a drawn-out band of cement is formed by tilting the rod toward

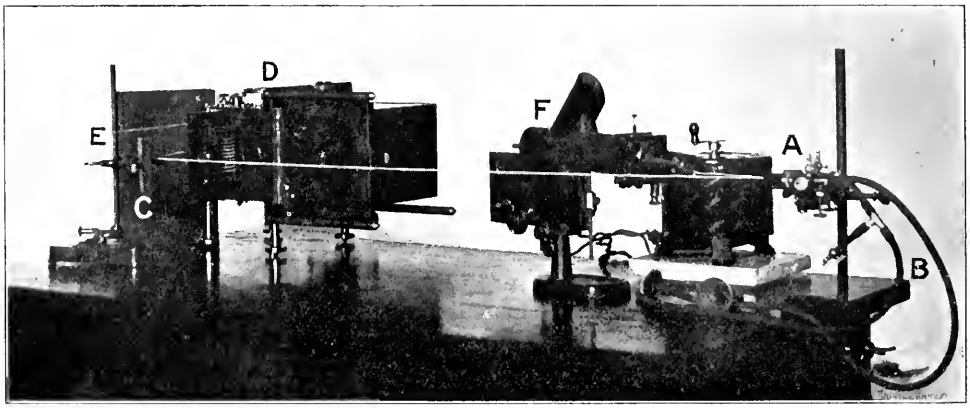

FIG. 6.—Photograph showing how two sound capsules may be aligned at right angles to a galvanometer projection. Description in text.

the horizontal plane. The open end of the segment capsule is now passed through this cement at right angles to the band. A thin film of uniform thickness will adhere to the edges and cover over the opening. After the rubber cement has nearly hardened the mirror is put in place so that it pivots upon the cord side. Care must be taken that the entire back surface of the mirror adheres. The mirrors used are very tiny, measuring 1.5 mm. by 2 mm., and weighing 0.2 mg. Obviously, they add but little effective mass to the delicate recording system.

In order that simultaneous tracings of the apex beat, supraclavicular venous pulse, or heart sounds from a different cardiac area may be taken, a second Frank capsule is attached to and horizontally aligned with the first capsule (Fig. 6). The type of

[13] Wiggers: Jour. Am. Med. Assn., 1915, lxiv, 1305.

membrane employed with the second capsule depends entirely upon the type of vibration to be recorded. The reasons for this have been detailed above. Suffice it to say that for coarser variations, such as the apex beat, light rubber dam is used, while for heart sounds the thinnest rubber cement film is made.

The Projection and Photographic System. With the capsules horizontally aligned a common beam of light is projected upon both. The capsules are so close together that the error in projection cannot be measured when the speed of the recording paper does not exceed 50 mm. per second. The most satisfactory source of the light beam has been a 5-ampère automatic arc lamp. The diverging rays radiating from the crater of the positive carbon pass through a lens which renders them parallel. These parallel rays in turn are cut down from above and below by an adjustable slot so that only a horizontal band of light emerges. Precision in focusing this band is accomplished by a final lens which focuses the positive carbon about 3 cm. in front of the capsule mirrors. Care must be exercised not only with the focus but also with the width of the light band. By comparing Figs. 5 *C* and 5 *D* it is seen how much to be preferred is the narrow light; in fact, it is possible for the sound oscillations to be less in amplitude than the width of a wide light band (*cf.* Figs. 4 *E* and *F*). In such a case the more delicate features are lost. The oscillations are recorded photographically by playing the vertically oscillating beam of light, as reflected from the mirror of the segment capsule, upon bromide paper moving horizontally at the uniform rate of 40 to 50 mm. per second.

When the electrocardiogram is simultaneously recorded it is essential that the arc lamp used for the capsules be in a position not parallel with the magnetic field of the galvanometer. This requirement precludes the possibility of throwing the three light beams directly upon the photographic paper. Either the two capsule beams or the light from the galvanometer must be deflected at an angle of precisely 90 degrees before passing into the photokymograph in order that a vertical alignment of the different records be preserved. For experimental convenience we deflect the galvanometer light.

It is probable that most workers having their galvanometer aligned with the photokymograph will prefer to deflect the capsule beams. The alignment for such an arrangement is shown in Fig. 6. The source of light is the arc lamp *F*. The light beam may be seen as it is projected upon the mirrors of the segment capsules *A*. Thence the rays are reflected upon the mirror *C*, which deflects them through an angle of 90 degrees into the slot of the photokymograph *D*. The light beam from the galvanometer is indicated by the string *E* as passing above the deflecting mirror directly into the photokymograph. Since this photographic arrangement requires vertical movements of the galvanometer string which actually moves

horizontally in its vertical suspension all of the rays emerging from the projection ocular of the galvanometer are rotated horizontally by a series of quartz prisms. If it is desirable to use a kymograph in which the paper film moves vertically it is merely necessary to arrange the capsules so that the mirrors of the segment capsules tilt in the same *vertical plane* and that a vertical instead of a horizontal band of light is projected upon them.

THE METABOLISM AND TREATMENT OF RHEUMATOID ARTHRITIS. FOURTH PAPER.

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In three previous communications,[1] the writer has presented a series of 37 cases of rheumatoid arthritis in which certain laboratory and clinical findings were made the basis of a method of treatment. The method in question consists essentially in the curtailment of diet, particularly the carbohydrates and proteins, to a point of tolerance which varies with the individual. In the last studies, experiments were reported, among other data, in which it had been apparently possible to induce exacerbations, in patients previously rendered free from the disease, by the feeding of pure carbohydrate.

The present article concerns further evidence in regard to the carbohydrates and, more particularly, evidence as to the role played by the fats; together with certain other findings. A series of 11 cases is therefore presented for the purpose of illustrating dietary experiments. No cases are here reported for the single purpose of illustrating further the therapeutic effect of a reduced diet alone, although such are available, as this has been done elsewhere.[2]

The plan has been followed here, in general, of determining the customary caloric intake of the individual as a help in ascertaining the reduction in food required, as elsewhere mentioned.[3]

From the caloric intake thus determined the respective proportions of protein, carbohydrate and fat could be approximated; in some cases very closely. In nearly all cases the diets which were followed, even the unrestricted "House Diet," were prepared according to fixed formulæ in which the above proportions are definitely known.[4]

[1] The Metabolism and Successful Treatment of Chronic Joint Disease; A Preliminary Report, Am. Jour. Med. Sc., October, 1912, No. 4, cxliv, 744; The Metabolism, Prevention, and Successful Treatment of Rheumatoid Arthritis; Second Contribution, ibid., December, 1913, No. 6, cxlvi, 895; January, 1914, No. 1, cxlvii, 111; February, 1914, No. 2, p. 265; March, 1914, No. 3, p. 423; The Metabolism and Treatment of Rheumatoid Arthritis, third paper, Am. Jour. Med. Sc., March, 1916, No. 3, cli, 351.

[2] Loc. cit.

[3] Loc. cit., number ii.

[4] Edwin A. Locke: Food Values.

In making the calculations of the proportions of carbohydrate, protein and fat in the ingested food, discrepancies sometimes occur between the caloric totals thus obtained and those calculated for the diet as a whole. These discrepancies are due to the omission from calculations of such foods as spinach, bouillon, lettuce and the like whose totals do not in these cases importantly influence the relative percentages. It will be seen that in the probationary diets and in the therapeutic diets, the proportions of the three ingredients, protein, carbohydrate and fat are practically always in such striking contrast that these discrepancies are negligible. Where more refined experiments could be conducted, these figures are exactly obtained, as in Case XLVIII.

In all of these cases, sources of possible infection had been removed before treatment was begun and all were examined for these by *x*-rays of teeth, sinuses, etc., by nose and throat specialists, by dentists, etc. In Cases XLIII, XLIV, XLV tonsillectomy was performed, on advice of the writer before considering dietary treatment.

The diagnosis of arthritis was corroborated in every case by *x*-ray pictures, taken mostly by Dr. William S. Newcomet, to whom the writer desires to express his appreciation.

Limitations of space preclude all but the barest outlines of the following cases except where a particular point is illustrated.

Case XXXVIII.—Mrs. S., aged about fifty years, referred by the courtesy of Dr. Hamilton Levings, of Milwaukee, was admitted May 18 and discharged July 3, 1916. The patient had a life-long tendency to "rheumatism" and presented a diffuse arthritis of three years' duration. There were very little soft tissue involvement and few objective signs of arthritis, and the condition seemed to concern largely the tendons. Unsuccessful attempts were made, analogous to those to be described later, under other cases, to replace the carbohydrate largely by fat, but her digestion was unequal to the task. After various reductions and fluctuations the diet was finally reduced for a few days to a mixed[5] one of 670 calories which was followed by distinct subjective improvement everywhere, but the patient could not be maintained on such a low intake. The diet was then increased to about 1000 calories, together with cod-liver oil, and this was followed with benefit though it seems plain that this case gave a definite but only limited response. During a period of unrestricted diet lasting six weeks she grew worse, developing effusion in the capsules of the finger-joints and improved, within limits, with subsidence of the effusion when the diet was again among reduced to about 1300 calories. It is perhaps safest to include this case among those instances which clinically fail to be benefited.

[5] By a mixed diet is meant one containing protein and fat in approximately the usual ratios, and carbohydrate in rather less than the usual ratio for the total caloric value as described in paper No. 3.

CASE XXXIX.—Mrs. R., aged about fifty-seven years, and referred by the courtesy of Dr. John W. Thornton, of Wheeling, W. Va., was admitted October 15, 1915 and discharged June 3, 1916. She was a wheel-chair invalid, with muscular wasting, secondary to widespread arthritis of seven years' duration involving nearly all joints and it was long doubtful whether dietary treatment could justifiably be attempted. This case is detailed chiefly because of observations on the urine to be mentioned later. The probationary house diet yielded about 2500 calories and on November 17, 1915, she was given a mixed diet yielding about 1400 calories, of which about 400 calories came from carbohydrates, about 200 came from protein, and about 800 came from fat. Almost at once this patient showed great improvement, felt less pain and the swelling of her hands progressively subsided. A difficulty of treatment presented in her easily disturbed digestion and the necessity of keeping up her general strength and weight in view of her invalidism. Because of this her diet was frequently interrupted and it was never possible to push it vigorously.

A *résumé* of this case in April, 1917, reveals the unmistakable influence of diet in an advanced case as shown by some return of function and decrease in swelling and pain. This case is still under observation and interpretation of the end result, as limited by the above factors, must be guarded but the arthritis *per se* falls unmistakably among the types susceptible of great benefit by these measures.

CASE XL.—Mrs. X., aged about fifty-eight years, referred by the courtesy of Dr. Frank B. Mitchell, of East Orange, N. J., was admitted April 12 and discharged June 3, 1916. She presented muscular pains together with an arthritis of practically all the joints of the hands. A probationary house diet yielded about 2500 calories per diem, of which about 1020 came from carbohydrates, 586 from protein, and about 633 came from fat. An attempt to feed this patient a large amount of fat was unsuccessful because of gastric indigestion, but after several modifications her diet on May 7, 1916, yielded about 1589 calories, of which about 376 came from carbohydrates, 153 from protein, and 819 from fat. This diet distinctly benefited her, but owing to her impatience the fat was first reduced, followed by reduction of the carbohydrate and protein until she was taking on May 26 about 1111 calories of a mixed diet.

On May 27 nearly every sore-point in her hands and elsewhere had improved and many had disappeared.

On June 3, the patient left the hospital prematurely against advice. Before beginning treatment her weight was increased 5 pounds by forced feeding, and on leaving the hospital it was exactly the same as upon admission.

CASE XLI.—Mary B., aged twenty-nine years, a ward case, admitted April 19, 1915, and discharged January 6, 1916, had a

diffuse arthritis of three years' duration incapacitating her. A reduced mixed diet of 1078 calories determined as in the other cases resulted in definite but limited improvement with loss of weight. After forced feeding and a large gain in weight she was given a diet of 1707 calories supplied by 300 grams of graham crackers, three apples, 21 grams of sugar and 5 grams of butter per diem. Practically all of the caloric value of this diet except for 120 calories was afforded by carbohydrates and she remained in active arthritis.

On December 30, 1915, this diet was changed to one yielding 1440 calories, of which about 1016 came from fat about 30 came from protein and about 378 from carbohydrate distributed as follows: Graham crackers 60 grams, 3 apples, 150 grams each, 30 grams of butter, olive oil 90 c.c.

On January 6, 1916, she insisted on leaving the hospital but applied for readmission in two days. She felt apparently quite well on leaving and on January 5 and 6 had walked considerably and freely. The objective evidence of improvement was subsidence of a fibrous nodule on the right ring finger and subsidence of the soft tissue involvement of most of the small joints. What the end-result might have been in this case cannot be prognosticated but there is no doubt as to the beneficial changes witnessed in the short period last indicated.[6]

Case XLII.—Miss C. M., aged fifty-six years, referred by the courtesy of Dr. John H. Musser, Jr., was admitted April 28, and discharged June 20, 1916. She had suffered from "rheumatism" for forty years. For five years the hands had been progressively involved and of late the knees and feet. On the house diet she ingested about 1581 calories a day of which about 851 calories came from carbohydrates, 323 from fat and 173 from protein.

On May 7, 1916, the patient was put upon a mixed diet yielding 1720 calories of which about 402 came from carbohydrates, about 183 from protein and about 1024 from fat. Thus the proportions of carbohydrates, and fat were almost reversed. After insufficient progress, on May 23 oil and butter amounting to 643 calories in all were removed from her diet, leaving a balance of 1077.

On May 26, 1916, there was some improvement, but as she was restless and impatient the diet was further changed by removing carbohydrate and protein to the extent of 227 calories, leaving about 850 calories. There was marked improvement and on June 4 she was holding her weight surprisingly well. The diet was then reduced to approximately 700 calories, and on June 7 she was better than at any time previously there being no objective sign of inflammation anywhere.

On June 20 her condition was so much improved that she felt she could follow her profession as a piano teacher. This patient was

[6] This patient was under observation only at the early and late periods of her stay in the Hospital.

seen by Dr. Musser on May 31 and June 13. Under protest she was allowed to follow this diet for a limited period at home under the supervision of the Social Service and was given cod-liver oil. Because of conditions at home she was unable to lead the quiet life advised and shortly had to be placed upon a larger dietary by Dr. Musser. This patient showed response to diet and became largely though not entirely free from symptoms while in the hospital where her weight fell from 128½ to 120 pounds. The end clinical result to her was *nil*.

CASE XLIII.—Mrs. N., aged about sixty-four years, referred by the courtesy of Dr. Horace Jenks, was admitted May 20 and discharged June 24, 1916.

This patient suffered from an arthritis of thirty years' duration involving nearly every joint. Tonsillectomy had been of no avail. On the probationary house diet she ingested about 1800 calories per diem which were afforded in the proportion of about 600 from carbohydrate, 333 from protein and about 700 from fat.

On May 26 she was given a mixed diet of about 1800 calories of which about 407 came from carbohydrates about 183 came from protein and about 1200 came from fat.

On June 1, improvement was noted but not knowing whether the fats were delaying progress 484 calories derived from olive oil were removed bringing the caloric total down to about 1334. Her progress was steady and on June 24 the sciatica and nearly all the tender spots in the hands had cleared up. She had had almost daily headache which disappeared entirely. The improvement in this case was beyond question, and the only real difficulty was in controlling her daily life. In the hospital her weight fell from 148 to 140 pounds. It is suggested that this might have been avoided by continuing the large fat intake and devoting more time to convalescence.

CASE XLIV.—Miss D. H., aged about forty and referred by the courtesy of Dr. John H. Girvin, was admitted March 25 and discharged June 29, 1916.

The patient suffered from arthritis of five years' duration involving the shoulders and knees, and the right elbow which could not be flexed beyond a right angle. On the probationary house diet she ingested about 1700 calories daily of which about 1026 came from carbohydrates, about 380 from protein and about 300 from fat.

On April 12, 1916, she was placed upon a mixed diet yielding about 1850 calories derived in the proportions of about 402 from carbohydrates, 118 from protein and 1318 from fat. The proportions of carbohydrates and fat were thus essentially reversed, the meat protein was reduced about 60 per cent. and the total calories were increased.

On May 1 the patient had made distinct though limited progress, best evidenced by less general soreness and increase of function at the right elbow which moved more freely than for five months

previously. She followed this diet religiously and in April, 1917, the situation could be summed up as follows: Periods of discomfort lasting for some days would be followed by weeks of bienaise in which she would be nearly free from all pain or stiffness. The periods of exaccerbation were marked by much less severe pain than she had suffered nearly constantly before treatment; and since treatment was begun the function of her right elbow had slowly but steadily increased. Particularly at night had pain been substantially modified and while she was not well it was clear that she had made unmistakable progress. During treatment the patient was given cod-liver oil. On admission and on discharge from the hospital she had a distinct secondary anemia, but in October, 1916, her blood count was normal. While in the hospital on the diet her weight fell from 114 to 105 pounds, from which it climbed to 112 pounds in January, 1917.[7]

Case XLV.—Mrs. M. W., aged about thirty-eight, referred by the courtesy of Dr. H. R. Wharton, was admitted January 24 and discharged June 26, 1916. This patient was anemic and suffered from a violent arthritis of about nine months' duration involving hands, knees and feet. Upon a probationary house diet the patient ingested about 2000 calories per diem yielded in the proportions of about 400 calories from protein, 1140 from carbohydrates and 602 from fat. On April 19, 1916, she was placed upon a mixed diet yielding about 2100 calories, of which about 488 came from carbohydrates, 233 from protein and 1400 from fat. The proteins were thus reduced about 50 per cent., the carbohydrates about 60 per cent. and the fats increased by about 100 per cent. A distinct improvement was noticeable, which with fluctuations continued until June 1, when it became less obvious. As a test of the value of fat, the bread in her diet was reduced by 60 grams a day which cut the caloric total down to about 1940.

On June 8 there was distinct improvement and the fingers changed their shape because of subsidence of inflammation. Although the evidence was not complete it strongly suggested that fat was the least harmful of the three dietary ingredients in this case. The loss of weight in the hospital was from 118 to 113 pounds. Improvement was maintained in January, 1917, as reported by letter.

Case XLVI.—Mrs. S., aged about fifty-two years, referred by the courtesy of Dr. S. McC. Hamill presented an arthritis of several years' duration involving all terminal finger phalanges. During the probationary diet she ingested an average of about 1723 calories, of which roughly 1000 calories came from carbohydrates, 400 from protein, and 275 from fat. She was then placed upon a mixed diet yielding about 1800 calories of which about 450 came from carbohydrates, 150 from protein and 1200 from fat.

[7] This case illustrates the time sometimes required for benefit to become established and also the importance of maintaining conditions invariable in such instances.

The figures in this case are not as accurate as in cases treated at the hospital as she weighed her food herself, under instruction but the respective proportions of the three food ingredients are correctly represented. She improved from the start and in two months all tender points were greatly improved and most of them had disappeared. The subsequent control of this patient was not satisfactory and she later disappeared from observation. Her loss of weight was from 225 to 205 pounds. She was seen by Dr. Hamill in June, 1916.

Case XLVII.—Miss M. S., aged about fifty years, referred by courtesy of Dr. Stewart Rodman, was admitted November 2, and discharged November 18, 1916. This case warrants greater detail and presented an arthritis of knees, hands, and jaws, with pain in muscle groups, dating back five years. On the probationary house diet she ingested about 2400 calories of which about 1200 came from carbohydrates, 215 from protein and about 900 from fat, leaving a small difference attributable to unreckoned calories from spinach, soup, etc.

On November 13th, she was put upon a mixed diet yielding about 2450 calories of which about 588 came from carbohydrates, 130 from protein and 1719 from fat. Benefit from this dietary was unmistakable and most gratifying. She progressed steadily and on December 17 was relieved of about 85 per cent. of her original symptoms. In fact, whereas she walked previously with much difficulty, could not get down upon her knees, etc., she was then walking as much as two miles a day with entire comfort. She still had occasional symptoms such as stiff neck in the early morning which would last for half a day, or a temporary exaccerbation in one joint, but only one conclusion was possible as to her general condition. A most interesting feature is the fact that in the period during which she followed the therapeutic diet her weight rose from $113\frac{1}{2}$ to $116\frac{1}{2}$ pounds a clear gain of 3 pounds. This was the first instance in which this has occurred in the writer's experience. This experiment shows not only that fat may sometimes be very well borne by these cases; and that in view of the reversal of the proportions of carbohydrate and fat in this case the harmful role of the carbohydrate becomes additionally evident; but it shows also that in selected instances it is possible adequately to maintain nutrition or achieve a gain in weight while the harmful elements in the diet are eliminated; no fat absorption experiment was performed but the stools showed no gross evidence of free oil. The gain in weight is substantial evidence of large, if not complete utilization of the ingested fat.

Case XLVIII.—Miss M. C., aged twenty-two years, referred by the courtesy of Dr. James E. Talley, was admitted November 12, 1916, and presented an arthritis of three years' duration involving the ankles, hands and wrists. This case was of great interest and yielded definite experimental data. The patient had been thoroughly examined for infectious foci and tonsils and several teeth had been

removed without improvement e ght months earlier. The probationary house diet yielded 1370 calories. On December 10 she was placed upon a diet of 1396 calories, consisting of 334 grams of graham crackers and 10 grams of butter per diem, of which about 924 calories came from carbohydrates, 123 came from protein and about 349 came from fat.

On December 20 she was worse and had lost $1\frac{1}{2}$ pounds.

On December 21 the experiment was started of greatly reducing her carbohydrates, keeping the protein about the same and increasing the fat to make the total caloric intake as high as before. Obviously if she improved on this diet it would indicate that the fat could be well borne and, further, that the carbohydrates were harmful. She was therefore started upon a diet consisting of 136 grams of graham crackers, 5 tablespoonsful of olive oil and 30 grams of butter per diem yielding about 1423 calories.

On December 24 there was distinct improvement but on December 27 she was still losing weight. In reducing the graham crackers from 308 to 136 grams the protein had been reduced by about 17 grams. In order to make up this protein deficit as a possible cause of improvement she was given three eggs a day in addition which yielded about 20 grams of protein and about 18 grams of fat making an increased total caloric value of 1675, of which about 408 calories came from carbohydrates, 135 from protein and 1132 from fat, total 1675. This was more in calories than she ingested on the house diet. There was no gross evidence of free fat in her stools and as evidence of the degree to which she had utilized the fat of her food can be mentioned her weight which rose upon this last diet from about 90 to 94 pounds.

On February 7, 1917, she was 95 per cent. relieved of all true arthritic symptoms, could walk well and close her hands well. There was distinct dimpling over all of the previously inflamed phalangeal joints, which were not tender to pressure, about the only remaining symptom being some pain on lateral motion of one foot which was pronated and rigid from faulty mechanics but had nevertheless shared the great improvement.[8]

In the work last reported attention was called to the fact that contemporaneously with natural or induced exaccerbations of the disease there seems to be a tendency for the urine to show a decreased acidity as measured by the hydrogen-ion concentration. The statement was also made that these findings needed corroboration for a longer series before they could be accepted as established. These observations have now been extended and it may be said that whereas this tendency toward a decreased acidity seems to be present in some cases, it is by no means always so. It apparently bears no necessary relation to subjective exaccerbations alone.

[8] Condition excellent, and weight $97\frac{1}{2}$ pounds on April 19, 1917.

Observations on the hydrogen-ion concentration were made for long periods in Cases XLI, XLIV, XL, XLII, XLVI, XLV, XXXIX, and XLIII but significant changes were observed in two only and in one case notably, XLIV, the hydrogen-ion concentration maintained a surprising concentration throughout notwithstanding marked fluctuations in the subjective sensations. None of these cases showed any striking objective fluctuations, etc., which may explain this constancy.[9] The cases above examined were all upon fixed and constant diets. With the idea of obtaining some picture of the metabolism as a whole at the time of an exaccerbation accompained by a drop in urinary acidity certain observations were conducted in Cases XXXIX and XLV. The results are given in the following figures. The hydrogen-ion concentration was determined according to the methods of Palmer & Henderson.[10]

The ammonia was determined by Folin's method, the nitrogen by the Kjeldahl method, the total acidity of the method of Adler and Blake[11] and the uric acid by the Folin-Shaffer method.

CASE XXXIX.

	Ph.	NH_3	NH_3 N. as per cent. of total N.	N.	
Jan. 11	6.15	..	..	..	Well.
12	6.15	0.2883	6.45	3.6803	Well.
13	6.7	0.1958	4.11	3.9084	Sick.
14	6.5	0.2082	4.7	3.7142	Well.
15	6.5	0.1763	4.14	3.5078	Well.
16	6.3	0.1926	4.62	3.4362	Well.
17	6.5	0.2633	6.28	3.4437	Well.
18	6.85	0.1905	4.36	3.5959	Sick.
19	6.7	0.1922	4.21	3.7585	Better.
20	6.7	0.1926	4.36	3.6382	Better.
21	6.15	0.2758	6.15	3.6909	Gastro-intestinal disturbance, joints pretty well, however.

It will be seen from the figures that in each case they reflect a drop in the hydrogen-ion concentration contemporaneously with the exaccerbation; this occurring twice in each case during the period of observation. In Case XXXIX the ammonia curve followed

[9] The drop in acidity may be referable to conditions accompanying effusion or other results of inflammatory processes.

[10] Walter W. Palmer, Lawrence J. Henderson: Clinical Studies of Acid Base Equilibrium and the Nature of Acidosis, Arch. Int. Med., August, 1913, xii, 153–170. The notation used signifies the logarithm of that number which expresses the actual acidity in terms of hydrogen-ion concentration; the logarithm decreases as the acidity increases and *vice versa* and the minus sign is omitted. It should be here stated that the logarithmic figures do not portray graphically the differences in reaction of the urine, as a drop from No. 7 to No. 4 in the scale of eleven flasks, three members of the series, is indicated merely by the change from 6 to 7 in the logarithm.

[11] Arch. Int. Med., 1911, vii, 479.

in general that of the hydrogen-ion concentration. The nitrogen behaved oppositely rising where the others fell and *vice versa*. In Case XLV much the same situation obtained; the total acidity and uric acid also following in general the curve of acidity.

CASE XLV.

	Ph.	NH_2	NH_3 N. as per ct. of total N.	Total acidity.	N	Uric acid.	
April 22	6.3						Well.
23	6.5						Well.
24 (1870 c.c.)	6.15	0.2034	3.2	269.2c.c. $\frac{1}{10}$ N.HCl	5.2360	0.2138	Well.
25 (2050 c.c.)	6.85	0.1952	3.055	176.4	5.2508	0.1576	Exacerbation.
26 (1930 c.c.)	7.0	0.2362	3.667	206.5	5.2959	0.1483	Still sore.
27 (1980 c.c.)	6.85	0.2154	2.961	186.0	5.9875	0.1141	About the same or slightly better.
28 (1880 c.c.)	6.85	0.2045	3.068	176.9	5.4745	0.1178	About the same.
29 (1615 c.c.)	6.5	0.2196	3.609	226.0	4.8837	0.1846	Better; less pain everywhere.
30 (1695 c.c.)	6.4	0.2305	3.844	254.1	4.9358	0.1938	Better.
May 1 (1635 c.c.)	6.5	0.2001	3.228	256.6	5.1274	0.1349	Feels pretty well.
2 (1800 c.c.)	6.85	0.1958	3.263	142.2	4.9392	0.2295	Very well. Drop unaccounted for
3 (1534 c.c.)	6.5	..	..	..	..	..	Stomachslightly upset but feels pretty well as to joints.
4	6.5	..	..	..	..	..	Well.
5	6.2	..	..	..	..	..	Well.
6	6.85	..	..	..	..	..	Exacerbation.
7	6.85	..	..	..	..	..	Exacerbation.

In Case XLII it was noteworthy that she withstood remarkably well the several low diets upon which she was placed holding her weight surprisingly as have other cases previously mentioned and in order to obtain a reflection of her nitrogen loss, a nitrogen balance experiment was performed upon her when she was taking a mixed diet of about 700 calories per diem as per the appended case history but it reflected nothing out of the ordinary. In seven days her nitrogen balance was as follows: Nitrogen outgo, 21.99; nitrogen intake, 16.87; nitrogen loss (urinary), 5.04.

In view of the experiments previously reported in which it was apparently possible to induce exacerbations in cases of rheumatoid arthritis, previously rendered free or nearly so from symptoms, by the ingestion of cane sugar, experiments were conducted upon the carbondioxide tension of the alveolar air in a series of normal and diseased subjects with the idea of determining any marked abnor-

mality in the rate or degree of utilization of carbohydrate by the diseased subject. Four control cases and five diseased subjects were studied two of the latter being in active arthritis and three of them well. The plan of procedure was to determine the carbon dioxide tension in the early morning upon an empty stomach, then to feed pure carbohydrate in the form of cane sugar in amounts varying from about 200 to 300 grams according to the capacity of the individual and then to watch the carbon dioxide tension at intervals of about twenty minutes throughout its rise and until it had returned to normal. This whole procedure occupied at least five hours and sometimes eight. The method used was the Plesch method as previously reported.[12] In addition some observations were made with the Haldane method using a valve, somewhat as suggested by Boothby and Peabody.[13]

In general the former method was the more dependable of the two. It was found in working with clinical subjects, especially beginning upon a fasting stomach, that the reliability of the determinations was influenced by the fatigue of the patient even when the latter was accustomed by repetition to the experiments. The aberent figures occasionally introduced were sometimes as widely fluctuating as those due to the rise in carbon dioxide tension and care was necessary to avoid misinterpreting them.

A series of 26 experiments was carried through *in toto*, some being repeated on the same subject. In some subjects consecutive uniformity was impossible. The following figures are from a normal case and one in active arthritis respectively:

Normal Case A. F., Nov. 11, 1916:		Case XLVIII, Active Arthritis, Nov. 30, 1916:	
Before sugar:		Before sugar:	
10.10 A.M.	45.806 M.M. CO_2	8.45 A.M.	34.361 M.M. CO_2
10.20 "	44.299 " "	9.5 "	33.649 " "
10.41 "	45.445 " "	9.30 "	35.499 " "
10.57 "	44.650 " "		
11.46 "	started sugar 287 gms.	10.4 "	started sugar 234 gms.
After sugar:		After sugar:	
12.30 P.M.	45.096 M.M. CO_2	10.40 A.M.	36.175 M.M. CO_2
12.55 "	44.156 " "	10.50 "	34.327 " "
1.42 "	44.879 " "	11.00 "	35.109 " "
2.20 "	47.698 " "	11.25 "	35.602 " "
2.45 "	46.180 " "	11.40 "	38.663 " "
3.00 "	50.213 " "	12.00 M.	34.043 " "
3.20 "	46.890 " "	12.15 P.M.	36.175 " "
3.40 "	47.107 " "	12.50 "	34.683 " "
3.55 "	45.589 " "	1.20 "	34.374 " "
4.15 "	45.289 " "	1.45 "	35.368 " "
		2.10 "	34.019 " "

Inspection of the figures shows that no immediate difference in the effects of large amounts of pure carbohydrate when ingested by

[12] The Metabolism and Treatment of Rheumatoid Arthritis, third paper.

[13] A Comparison of Methods of Obtaining Alveolar Air, Arch. Int. Med., March, 1914, xiii, 497-506.

normal and by diseased subjects is reflected in the carbon dioxide tension, at least under the conditions of experiment.

It is a pleasure to acknowledge the assistance of Miss E. C. Titlow in making the observations on alveolar air.

Discussion. Consideration of the above cases reveals some interesting points. In the first place it is clear that the ingestion of fat by arthritic cases treated in the above manner may result differently from the ingestion of carbohydrates. It has appeared from a study of the present series that fat could be ingested with benefit in larger amounts than could carbohydrate but it has remained for the last two quoted experiments to indicate this definitely. In two cases where a large amount of carbohydrate was ingested during a period in which the patient remained ill, this amount of carbohydrate was reduced by approximately two-thirds and then replaced entirely by fat. In one of these cases the protein intake was increased with the increase of fat and in the other it was somewhat reduced. Coincidentally with this change in diet there occurred in each case an amelioration of symptoms which was beyond all question and in sharp contrast to the preceding condition of health. It is of the highest interest to note that each of these cases gained weight. It might be alleged that whereas reduction of carbohydrate had been beneficial the increase in fat was not clearly so, and not even harmless, because of the possibility that it had passed through unutilized. No fat absorption experiments were carried out but it seems clear from the maintenance, let alone the gain, of weight, coincident with the sharp reduction in carbohydrate, that the fat must have been largely if not entirely utilized. These experiments indicate therefore not only that fat is much less harmful, than carbohydrate, if indeed fat per se is harmful at all, but they also additionally indicate that the carbohydrates themselves are a cause of arthritis especially since the third element of diet, protein, was actually increased in one case.[14]

In only certain selected cases where the disease is not hopelessly chronic and the age and condition of the patient are such that lessened activity of the arthritis can be clearly appreciated, can such experiments be carried out. Furthermore gastric and intestinal digestion must be quite equal to the digestion of fat in such large quantities as are necessitated in this "experimentum crucis." Again, the reduction of carbohydrate required to influence the arthritis must be relatively moderate so that the caloric value removed may be replaced by that from fat. It is also essential that the probationary unrestricted diet shall properly reflect the nutritive equilibrium of the subject and itself be not too high in caloric value for this level to be approximated later by the addition of fat.

[14] Two other experiments in which the protein was increased by a considerable margin have since apparently further indicated this. It will be noted that there is here some evidence that a relatively minor role for evil is played by protein.

The use of fat in such large quantities is not necessarily a clinical desideratum, even when the experiment can be carried out, and was for experiment only. For the reasons above given the evidence from the series reported, although suggestive, was not conclusive as to the possibility of what could be accomplished under favorable circumstances until the last experiments. Even in the less satisfactory types, however, such as the first nine of the series here quoted it is fairly clear that fat can be used with more or less satisfaction to the nutritive necessities. The difficulty of obtaining circumstances favorable to experimentation determines the reporting of these cases now. In advanced cases such experiments are often not clear cut and it seems possible that factors other than those originally causing the arthritis enter into the problem. It would then appear necessary not only to cut off largely the supply of toxin which caused the arthritis but additionally to influence various tissue cells, particularly perhaps in the muscles, to "utilization" of these products. Thus it appears from the study of a number of cases that a diet which is beneficial at the start in a severe case and is accompanied by a loss of weight may, after a time, operate less favorably and that a still lower diet and a further loss of weight secondary to it are required before improvement is again apparent.

In these instances it is conceivable that conditions within the tissue cells, the muscles for example, may then approximate the condition of so-called "basal metabolism" or even conditions of starvation. Under such circumstances the products of normal or pathological metabolism which reach them may be better handled or removed. This has been an hypothesis in the treatment of diabetes which recently has had confirmation. The corollary to this principle possibly explains the beneficial action, within limits, of radium, arsenic, thyroid extract and *x*-ray, the tissue cells in these instances being "whipped up" to some sort of heightened metabolism or activity by these agents. Only in the event that such heightened cellular activity could keep pace with the access of fresh toxin would these agents prove of value on this hypothesis.

There can be no question furthermore from clinical grounds alone that in certain borderland cases exercise importantly influences the "rheumatic" symptoms and it is conceivable that the modus operandi here is much the same and depends upon the "utilization" of intracellular substances.

The use of diet as advocated in this condition is not indefinite as directed toward thinning the fat individuals and fattening the thin, but specifically to reduce a source of toxin. The possibility remains that in some unknown way reduction in diet may modify the flora of the intestine and that this modification may result in changes in their elaborations. There may be a reduced quantity of bacterial split products of carbohydrate and protein. Again the benefits of a reduced diet may be referable to the actual metabolism of the

tissue cells themselves and the lessened demand upon them. There is strong ground for believing that whatever the mechanism within the intestinal tract this last factor also plays a definite role. Whether or no the mechanism concerned be in fact that of bacterial activity within the intestine the method described affords a means of controlling the pathological process secondary to it.

Among attempts made to determine whether bacterial activity is a factor here was the administration of capsules of trimethol a substance[15] which is alleged to inhibit bacterial activity without interference with digestion or any toxic results from the substance itself. This was given a trial in Cases XXXVIII and XLIII but with no benefit.

Certain other points deserve mention. It is interesting to note that bone changes may apparently precede the clinical symptoms of arthritis. Not infrequently the *x*-ray will show changes, along the shafts of the bones, which give no clinical symptoms and have existed presumably longer than the joint trouble of which the patient complains. In some instances showing acute involvement of the finger-joints of only one, three or four weeks' duration (Case XXXIII) *x*-ray of the phalanges may show these overgrowths and rarification which would seem to be of longer standing. Furthermore in certain cases the subject of headache, neurasthenia and other conditions not apparently related to arthritis and having no clear etiology, *x*-ray may show the same changes. In the absence of a history of arthritis or "rheumatism" this can sometimes be regarded as a symptom of an underlying disturbance having something in common with arthritis.

Some such cases treated along parallel lines have borne this out in their clinical response, and it is suggested that in such doubtful cases the *x*-ray may yield important evidence as to the nature of the underlying trouble. Again in certain cases where there is doubt as to the exact nature of an arthritis, in the knee for example; when there are no other joints involved and the process seems local; *x*-ray of the hands may show a striking and surprising degree of involvement which at once proves the arthritic process to be widespread and systemic. In such doubtful cases it is well to include routinely *x*-ray of the hands.

It is something of an argument for the identity of the several types of arthritis, atrophic, hypertrophic and mixed, that they may all respond to diet including the fibrous nodules. These last may disappear entirely. The type of arthritis which seems to respond less well or sometimes not at all to these dietary procedures is the so-called dry type[16] of primary progressive polyarthritis, involving the tendons rather than the other periarticular structures.

[15] Thomas Leaming & Co., New York.

[16] Lewellyn F. Barker: The Clinical Diagnosis of Internal Diseases, Monographic Medicine, iv, 93 *et seq.* D. Appleton & Co., New York and London.

It is noteworthy that some cases of long standing involving clinically nothing more than the terminal phalangeal joints of the hand respond with as much difficulty as though more important joints were concerned and the whole health of the individual reduced in consequence. In other words the limited extent of an arthritis does not necessarily imply facility of treatment and conversely a widespread involvement may subside surprisingly easily.

It should be borne in mind in considering responses of only moderate degree that they occur for the most part in patients the subject of chronic arthritis, generally of poor nutrition, and in the later decades of life. It is of course precisely the most advanced and difficult cases which are most ready to take up treatment and exceptionally is there opportunity to treat arthritis unaccompanied by sequelæ.[17] It is important again to emphasize the necessity of caution in carrying out treatment along these lines, as elsewhere discussed in detail.

Conclusions. 1. Experiments are cited in which it has been possible to relieve patients of all or practically all, symptoms of diffuse arthritis by a large curtailment of carbohydrate coincidently with the ingestion of fat in such increased amounts as to make up or exceed this caloric deficit. When the protein intake has been kept approximately constant some such patients have actually gained weight while convalescing. This evidence by exclusion ascribes an injurious role to carbohydrate, is additional to that already published and is corroboratory of it.

2. It is difficult to avoid the conclusion that fat, while it cannot be used with impunity in treating these cases, plays a relatively harmless role in marked contrast to carbohydrate. It can apparently be used in many cases to meet, more or less, the loss of weight which would otherwise ensue and in certain selected cases to meet it entirely or even to cause the patient to gain weight.

3. The difference in the effects of large amounts of carbohydrate when ingested by normal individuals and by subjects of rheumatoid arthritis is not reflected in the carbon dioxide tension of the alveolar air under the limited conditions of the experiments.

[17] The exact proportion of cases in which clinical benefit may be expected, cannot be given, but is indicated in general with some of the determining factors in the third paper, loc. cit.

THE SYMTOMATOLOGY AND TREATMENT OF ARTERIOSCLEROSIS.[1]

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It is not my purpose to go into the more complicated scientific aspects of cardiovascular disease, but to give a practical analysis of the problem as determined by the essayist's experience and the experience of men in practice. The writings on the subject are voluminous and the unsolved truths are legion. The facts known about what the disease is in its development, its causes, and its manifestations, are far outweighed by speculative theories; so that even though the condition has long been recognized, our knowledge of its intricate processes is as yet in the field of experimentation and discovery.

Galen was the first to refer to the character of vessels, their softness and hardness, but not until comparatively modern times have we had an appreciation of arterial disease. Morgagni was the first to throw any light on the subject and the discovery of the circulation by Harvey led to a consideration of blood-pressure. Blood-pressure was first estimated by Hales, in 1727, in glass tubes, and the mercury column was not brought into use until about one hundred years later. The term arteriosclerosis was adopted by Lobstein in Paris in 1833, and it was von Basch, of Vienna, who by animal experimentation and clinical observation laid the foundation of our present-day knowledge of the problem of arteriosclerosis. In 1879 Mahomed, of Guy's Hospital, London, recognized the importance of rising blood-pressure and introduced the term pre-albuminuric stage of Bright's disease, which corresponds with the presclerosis type and the hyperpietic type of modern authors. Virchow, in his *Archives*, was the first to place arteriosclerosis on its modern basis.

The problem of blood-pressure is not well understood, and today we are unable to say just what a normal blood-pressure is. However, there are many facts that we do know. We know that pressure rises with advancing years, that at birth, systolic pressure is in approximate range of 35 to 55, and that a systolic pressure of over 150 at middle life is not normal. We know that systolic blood-pressure tends to rise with advancing years, but diastolic rise is not proportionate; hence an increase of amplitude or pulse-pressure. It is impossible to formulate a normal curve of daily life, for so many mental and physical factors enter in that we

[1] Read by invitation before the Northern Tri-State Medical Association, Toledo, Ohio, January 10, 1916, and Twelfth Councillar District of Indiana, Fort Wayne, Ind., April 12, 1917.

cannot weigh accurately; so, at best, blood-pressure determinations can only be approximate. We know that we can have markedly sclerosed vessels with low blood-pressure and very high blood-pressure without evident sclerosis, so that pressure elevation does not necessarily depend upon sclerosis. Even though blood-pressure be only an approximate determination we have come to value the instruments of precision in its determination so that the auscultatory method of determination of both systolic and diastolic pressure has become a routine in practice. The normal diastolic pressure under middle life is approximated at 80 or 90 to a systolic of 125, and if over 90 is considered abnormal; then the ratio is diastolic to systolic as 3 to 4 and the pulse pressure to systolic as 1 to 4. The factors bearing on blood-pressure, both static and dynamic, are so complex, such as the volume of wave, the pressure, the tone and density of walls, the big pulse with low pressure and the thready pulse with high pressure, the effect of meals, the time of day, the temperament or training of the individual, the viscosity of blood, lung capacity, the hormones, etc., that certain able experimenters doubt the value of all or any scientific gauge of blood-pressure, and if such be true, our finer distinctions or deductions made from changes in pressure must be more or less speculative.

The modern tendency is not to regard arteriosclerosis as a disease but as an anatomical result of various pathological processes. A clinical classification given by Allbutt and accepted by Osler is: (1) high pressure arteriosclerosis (hyperpiesia and chronic renal disease); (2) involutionary or decrescent (senile); (3) infectious or toxic (typhoid, syphilis, diabetes, lead). Hyperpiesia (Huchard's presclerosis, von Basch's latent sclerosis) goes over a period of forty to sixty years of age with an average duration of ten to twenty years, and this is the type that brings death by cerebral hemorrhage or cardiac defeat. The decrescent form or senile form of arteriosclerosis begins at fifty or sixty and exists over an indefinite period. In either form chronic renal disease may be present, but not necessarily so. Observation has shown that arteriosclerosis may uncommonly occur in early life. Von Romberg observed a case at the age of twelve years. Autopsy work in asylums has shown degrees of sclerosis not to be uncommon in young people. However, its character is fibrous rather than atheromatous. These cases are considered infectious in cause, and syphilis plays no small part aside from the acute infections and tuberculosis. The causes of arteriosclerosis are not within the scope of this paper, and I shall take up a consideration of the symptomatology. Adami says arteriorenal problems are the most complicated and obscure in the whole of pathology, and if this be true of pathology it must be equally true of etiology and symptomatology.

Just what part the kidney plays in cardiovascular disease is not

known, for our observations have been incomplete—autopsy findings have come too much in the terminal stages when the processes have been made obscure. In discussion of symptoms we will keep in mind the simple classification into two types, viz., the hyperpietic and the involutionary or decrescent form. The hyperpietic form may occur, in fact more often does occur, independent of primary renal involvement, and is the type of case that the German school terms essential hypertension. However, there is another group of cases under this type of hypertension without evident sclerosis that is secondary to renal involvement, and this group the Germans term nephritic hypertension. Osler as far back as 1898 referred to this classification. Prof. Krehl, of Heidelberg, whose authority in these problems is beyond question, says we tend to attribute all cases of high blood-pressure to nephritis, which is untrue. Stengel says that albuminuria in arteriosclerosis is not necessarily evidence of Bright's disease. Tyson and Janeway are of the same opinion. Kidney function tests, careful clinical observation in conjunction with pathological investigation, promises to give us a more definite understanding of this problem. In the decrescent form of arteriosclerosis the form that shows the sclerosed and atheromatous arteries with low blood-pressure frequently, the kidney process is the arteriosclerotic type more often and is not necessarily a badly diseased kidney. Osler refers to traces of albumin in elderly persons, and asks how many persons over fifty have kidney histologically normal. The red granular kidney always gives a definite hypertension in contradistinction to the arteriosclerotic kidney, which is atrophic and is associated with low pressures. Mahomed was the first to recognize that certain cases of hypertension were not associated with renal disease, but considered them pre-albuminuric states. We now know that albuminuria in association with hypertension is not necessarily Bright's disease.

Janeway found in making observations on 130 cases with blood-pressures above 200 that 17 gave no evidence of renal involvement, and later he says autopsies tend to prove that hyperpietic kidneys give little or no evidence of change. It is the hyperpietic case that bears venesection well and is improved while the kidney involved case is not. Arteriosclerosis is a resultant of many diseases and conditions and does not in itself give any specific symptomatic series. It has no uniform symptoms of its own, unless we accept the hypothesis of Virchow, who considered it an inflammatory process—an arteritis. He regarded it as an inflammatory disease of the arteries having a definite course with which was associated a slight temperature rise. Allbutt regards the symptoms of arteriosclerosis a tangled skein, some of which have been combed aleady into order and others remain confused. Von Basch considered hypertension to be caused by sclerosis, and when not recognized

in palpable vessels thought it to be regional, such as splanchnic. The same opinion was held by Huchard, who maintained that presclerosis was immediate on sclerosis. The hyperpietic case may be without symptoms other than hypertension. When dyspnea and sternocardia are evident the case is no longer early. There is no question but that a hyperpietic case can be detected when it is curable. The common subjective symptoms in association with hyperpiesia are substernal distress on exertion, transitory hitches in speech, vertigo, numbness of extremities, sometimes transitory paresis of hand or arm, tendency to tire, mental depression, insomnia, headache, irritability, and often signs of nervous dyspepsia. If asked to describe his symptoms the patient's story is often vague; he is cognizant of ailing but scarcely knows how, and feels the need of stimulation. It is this type of case that is often loosely diagnosed neurasthenia. The pulse-rate may or may not be increased but has a suggestion of hypertension and extrasystoles are often present.

The heart shows a degree of hypertrophy, more particular of the left ventricle, with accentuated aortic second sound. Later, hypertrophy gives way to dilatation and mitral insufficiency is made evident. The palpable arteries will have become thickened and tortuous. The large veins on hands show distention, and slight edema may be found on the anterior tibial surfaces. The urine may show traces of albumin without formed elements. The aorta is often dilated and the second sound becomes much clearer as it approaches the surface of the thorax. The elongation of the aorta permits falling of the heart base, so it assumes a more horizontal position, which throws the apex out. When atheroma is present the second sound may become more metallic. An accentuation of the aortic second must be differentiated from nervousness, and when normally the vessel is near the chest wall. Pulsus alternans is occasionally observed. These arrhythmias are supposed to be caused by increased irritability of the heart muscle under strain of hypertension, and are relieved by reduction of pressure. Galloping rhythm is occasionally present. In some cases the aorta may be palpated in the episternal notch. The two radial pulses may show differences which suggests invasion of the subclavian by the atheromatous process. It is impossible to differentiate the syphilitic type of aortitis from the arteriosclerotic in behavior, but pathologically the syphilitic more often invades the ascending portion of the arch. A widened aortic area on percussion is very commonly made out. Attacks of dyspnea are very common and are rather instantaneously relieved with nitroglycerin; the same is true of anginoid pains. However, some authorities take exception to calling them anginoid and use the term cardiac pain. A large percentage of these cases show tenderness on percussion over the precordium. In the paroxysmal dyspnea of high

pressures, pulmonary edema is often associated. Emphysema is more commonly associated with the decrescent type of arteriosclerosis. Bronchitis is more common in the hyperpietic type. Migraine is not uncommonly a forerunner of the hypertension type, but in the associated head pains, cerebral syphilis must always be considered. The vertigo of arteriosclerosis is supposed to be aural in type. Epileptoid seizures are not uncommon in arteriosclerosis, especially the hyperpietic type, but here one must differentiate a degree of uremia with brain edema. Cerebral hemorrhage is the most serious aspect of hyperpiesia, for it often occurs before subjective symptoms and before vascular change is evident. The only warning may be transitory numbness or slight mental confusion. These transitory phases may well be called intermittent claudication or angiospasm, and are more often associated with the hyperpietic type while aphasia is probably with the decrescent type. One not infrequently observes rather profound apoplectic seizures that regain consciousness and improve decidedly. No doubt this type case sustained a local brain edema or spasm of cerebral vessel (but this is questioned by certain authorities) or punctate hemorrhages that are not extensive. Molecular fatigue has been advanced as a probable cause of such attacks. Osler regards these attacks of paresis, which are transitory, as resultant of vessel spasm, on the grounds that sclerosis encourages spasm. Russell holds the same opinion. Allbutt disputes this theory and says that the sclerosed vessel is less subject to vasomotor change than the normal vessel, and if such a cause were true we would have such phases frequent in normal individuals, and says that death in coma is due to increased intracranial pressure, which is not increased by constriction of a vessel. Cases autopsied where these transitory phases were historical and where death was caused by apoplexy show numerous old punctate hemorrhages.

Forbes Robertson says that after months or years minute hemorrhages may be represented only by tiny sclerotic patches, and in brains of the insane such islets are often seen. The French have observed in doing repeated lumbar punctures in cases of high blood-pressure, the fluid is often bloody and shows signs of old hemorrhage, but 20 to 25 c.c. must be taken out to discover blood cells or hemoglobin. Other observers think these hemorrhages are due to hemolytic toxins, but this occurs in the nephritic type. The advisability of bleeding in an individual case of apoplexy is difficult to determine, and it is often remarked that it either kills or cures. The symptoms of the decrescent or involutionary type of sclerosis may be *nil*, and this condition may not be incompatible with long years. Emaciation is generally evident and may be cachectic in character. When palsies occur they are atrophic and not hemorrhagic. This type of case is very commonly found in our asylums. The kidney is fibrosed and is a part of the general

degenerative process. Softening of the brain occurs in this type, and such an arteriosclerotic may exist for years, so that the old saying that a man is as old as his arteries is not quite true. Hemorrhage is not common, but infarct emboli and thrombosis may occur. A large percentage of these cases show eye-ground changes. Such a patient's mental state is different from the hyperpietic's in the fact that he becomes more or less passive while the hyperpietic is given to spells of depression. The heart of the decrescent type is atrophic, in contradistinction the hypertrophic heart of the hyperpietic type and the decrescent type rarely meets the cardiac defeat which is common in the hyperpietic. Arteriosclerosis advanced has no treatment, but the state of high blood-pressure which may be regarded presclerotic has. While it is not within the scope of this paper to consider causes, we cannot rationally discuss treatment without briefly considering etiology at least in a speculative way. The rise of blood-pressure in the hyperpietic must be due to increased peripheral resistance, and this must result from narrowing of the peripheral arterial tree or increased viscosity of blood, or both. The constriction may be due to disordered metabolism or intoxication, which may act directly on the vasomotor centre or upon the vessels themselves. Hyperpietic states are amenable to treatment if taken early. Hence, our problem is to determine the degree or time of existence. The early case when put at rest in bed, with encouragement of elimination, for a period of time, if favorable, will show a definite lowering of pressure, a lessened accentuation of the aortic second and a lessening of cardiac hypertrophy. I am sure it is the experience of everyone who has observed these cardiovascular cases to not uncommonly find a return to apparently normal after an unfavorable prognosis had been given. If this supposed early case does not respond to such management then we must conclude that the vascular system has sustained stresses that are not amenable to management and therefore the prognosis becomes less favorable. These patients must not be treated at the expense of their well-being. It requires extreme tact in rightly managing them, for there is a tendency to live around the blood-pressure and become very introspective. Immediately they regard themselves as candidates for apoplexy. They very quickly label themselves as high blood-pressure victims and become intensely neurotic. The blood-pressure estimations must always be favorable to their improvement. Here truly can we say that blood-pressure is a very changeable thing; that its determination can never be made definite; that our means of estimating are only approximate at best; that blood-pressure is a minor thing; that the condition as a whole is our chief concern. It is our duty to take the patient from all strenuousness of life and discipline him in a régime which is favorable to improvement, for after all the problem is one of man-

agement rather than a particular drug. We must restrict the diet, particularly in respect to meats, condiments, stimulants, sugars, and fats. If obese, the cardiovascular mechanism will be relieved by reduction in weight. Many patients are greatly improved in subjective symptoms, such as dyspnea, cardiac pain, and fatigue on reduction of weight, which gives a corresponding and often disproportionate reduction in blood-pressure. In severe cases with obesity reduction may best be managed by rest in bed over a period of months. Overeating, directly or indirectly, is a factor of no small importance in producing cardiovascular disease, be it due to putrefactive substances from the bowel or overtaxing of excretory organs by unused food material. I shall not enter into a detailed discussion on a dietary, as certain principles in feeding are to be observed with which we are generally acquainted, and the problem is more or less an individual one. Just how much or how little salt may be given in an individual case is often speculation. However, we do know that withholding salt in cases with edema or pre-edemic states gives encouraging results. Careful dietary, management, and well-regulated exercise will do much in the early cases of hyperpiesia, and no kind of exercise is better than walking. In the more advanced cases a period of rest in bed is essential, with warmth, passive exercises, and baths. A mild and equable climate with moderate elevation is desirable. Excessively hot baths are generally not beneficial and do not give substantial relief, and may give the patient discomfort. The desirable bath seems to be neutral at about 33° or 34° C., and gradually brought to 40°. Nearly all baths affect the cardiac mechanism and should be given cautiously. The advantages of treatment aside from careful regulation of diet, encouragement of elimination, and gradation of activity are probably overestimated. Authors disagree on value of warm or hot baths, but the tendency is to get away from the hot bath. The quantity of water taken depends upon the individual case; but speaking generally the liquid intake of the hyperpietic case should be restricted to $1\frac{1}{2}$ or 2 liters daily. The radium bath (natural water) has become popular in the management of these cases. It is claimed that it lessens viscosity of blood, increases diuresis, and encourages uric-acid elimination, and hence lowers blood-pressure. Electric-light baths have been advised but should be used in the same careful way as tub baths, starting at lower temperature and gradually increasing to 90° or 100° F. Electricity in the way of high-frequency currents is advised by some and discouraged by others. I believe the consensus of opinion is that it lowers peripheral resistance and, of course, lowers pressure. Venesection is of value in the high-tensioned case, is of value in warding off a crisis, and may be repeated at intervals in certain selected cases. It is a very simple procedure by placing a towel as a tourniquet above the elbow, tapping the space at the bend

of the elbow to bring out the vein, scrubbing with alcohol, and inserting a needle of sufficient lumen to permit a free flow, which is encouraged by having the patient alternately close and open his hand. Bleeding is contra-indicated in cases of high pressure, with kidney involvement when there is a degree of anemia. The blood-pressure is lowered for only a short period, but a sense of relief is experienced from their pressure symptoms. It is contra-indicated in the decrescent form with low blood-pressure. In treating blood-pressure we must appreciate that the process is largely compensatory, and our interference should be cautious. Therefore, insofar as vasodilator drugs fail to relieve a cause as a toxin we must consider how much lowering of pressure in this way brings about good. However, if our experience teaches us that symptoms can be relieved and the patient be given no hazards, symptomatic treatment is justifiable, and so long as we are unable to prove that their high pressures may be due in part at least to toxin irritating the vasomotor centre, it seems quite rational to give vasodilatators, such as nitrites, even over an extended period of time if pressures are lowered and the patient is made more comfortable without untoward signs, such as edema or a failing myocardium. Nitroglycerin in drop doses has a definite place in relieving cardiac or anginoid pains, and I not infrequently place it in a patient's hands to be used cautiously when indicated. Just how so-called vasodilatators act is speculation. It is accepted that diastolic pressure is lowered, and the question is whether by peripheral dilatation or splanchnic dilatation or by lowering cardiac energy. We should watch not only our systolic but diastolic pressure when administering such drugs. At best, drug therapy is only an adjunct to the treatment of these cases. Mercury is employed, but in the non-syphilitic case I have had no experience. Iodids unquestionably have value if given intensively over a period of time with alkalies even though animal experimentation is to the contrary, but we cannot compare normal with abnormal arteries. Just how is speculation, whether by lessening viscosity of the blood, by lessening spasm, or by excitement of the thyroid. The iodids may be given in combination with bromids. For a failing heart no drug is superior to strychnin. Diuretin is used in cases of anginoid pains, but I have seen no benefit from its administration. I have no experience with the antisclerotic serums, and the general impression is that they are useless. Aspirin and sodium salicylate lower pressure and have some value. Vasotonin, which is a combination of yohimbin and urethane, has not proved useful. Fibrolysin as having value is a question. Thyroid extract seems to be of little or no value. When unable to relieve peripheral resistance against a failing heart, digitalis is indicated. A good index is to administer digitalis when the diastolic pressure is rising and pulse-pressure lessening. Strophanthin or strophanthon may be employed, but

at times are toxic. The principle to be adhered to in the treatment of arteriosclerosis is not the sclerosis but the morbid changes, be they toxic or otherwise. In the senile type we have nothing to treat because it is as natural as gray hair or arcus senilis. On general principles tonic treatment is indicated, and if hyperpiesia should develop, they should be managed as the hyperpietic.

FOCAL SEPSIS IN THE GENITO-URINARY TRACT AS A CAUSE OF CONSTITUTIONAL DISEASE.[1]

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The importance of focal sepsis in its relationship to the genito-urinary tract entitles it to a prominent position in the minds of internests, general surgeons, and the various specialists.

Among the numerous septic affections involving the genito-urinary system which, untreated, are prone to lead to constitutional involvement may be mentioned acute hematogenous suppurative nephritis, pyelitis, pyelonephritis, pyonephrosis with or without calculus, tuberculosis of the kidney, renal, and perirenal abscess, ureteritis, cystitis, especially the purulent type, prostatitis, seminal vesiculitis, epididymitis, orchitis, and urethritis.

I have observed patients who have spent large sums for the correction of pyorrhea alveolaris and other dental disorders, when the real cause of complaint was centered in chronically diseased seminal vesicles. I have heard of a case on whom hundreds of dollars were spent for extensive crown and bridge work, when seminal vesicle medication and massage, or vesiculotomy or vesiculectomy, would undoubtedly have sufficed to eradicate the constitutional affection from which the patient suffered. I have treated patients, previously subjected to tonsillectomies unattended with benefit, so far as the chief indication for their performance was concerned, and observed immediate improvement when measures were directed to the diseased seminal vesicles. I have seen patients complaining of rheumatism, investigated by elaborate metabolic studies and placed on restricted diet lists, when vasopuncture and spermatocystic medication, or drainage of a seminal pyovesiculosis, would doubtless have effected a cure. How many patients treated by the general practitioner, or for that matter by the internest, the general surgeon, the orthopedist, the neurologist or the psychiatrist, in our best hospitals, complaining of symptoms

[1] Read by invitation before the Philadelphia County Medical Society, April 12, 1916, and received for publication June 11, 1916.

possibly referable to diseased urethral adnexa, ever receive an examination by rectal palpation, etc., or if so by any one really qualified to express an opinion? Assuredly, the average hospital resident, to mention the least, knows little or nothing, clinically, about inflammatory prostatic involvement, much less disease of the seminal vesicles. The above assertions are made in no spirit of vindictive criticism, but solely with the desire and hope that the profession generally may be awakened to a realization of the fact that chronic seminal vesiculitis is a far more prevalent disease than the average physician surmises, that it is not accorded the consideration its medical importance demands, and that it masquerades under a manifold symptomatology finding its expression ofttimes remote from the urinary tract. In view of the high percentage of the male population who have had gonorrhea, and realizing that 90 per cent. at least of these have had posterior urethral involvement, it must be apparent to everyone that, comparatively, there are few men who have not experienced a spermatocystitis.

The time has arrived for every practitioner of medicine to recall the anatomy of the spermatic tract—vesicle, ampulla of vas, and ejaculatory duct. Three facts stand out preëminently: (1) the tortuous nature of these tubular structures, presenting an extensive mucous surface fitted with ramifying diverticula, characterized by minute cellules and ridges, rendering the tract, when infected, the worst drained of any in the human body; (2) a most complex and delicate nervous mechanism, filaments from the hypogastric plexus penetrating intimately the muscular and mucous coats of these delicate spermatic tubular structures. Thus owing to the correlation of the prostatic, vesical, pelvic, sacral, lumbar, and hypogastric nerve plexuses the occurrence of pains referred to the anal, perineal, genital, hypogastric, and lumbar regions, also to the hip-joint, sacro-iliac synchrondroses, and the thighs, becomes readily explainable; (3) the gross anatomical relationship, rendering these structures, on account of a more or less inaccessible situation, difficult of treatment, either conservatively or radically.

It is almost incredible that the seminal vesicles so closely associated with the prostate should have escaped so long consideration in investigation of the pathology of deep urethral infection while the prostate has been so thoroughly studied. Indeed in text-books, universally, the vesicles have been alluded to casually or entirely neglected; yet I believe that they share in infection equally as often as the prostate, and are far more prevalent septic foci as causes for certain neurological and constitutional disorders.

Epididymitis is always associated with a spermatocystitis on the affected side, and recurrent epididymitis is invariably caused by a lingering infection of the seminal vesicle. The gleety discharge of a protracted gonorrheal infection is commonly due to a latent infec-

tion of the spermatic tract—the shreds originating in the vesicles—rather than a chronic process located in the prostate or posterior urethra.

As a pure gonorrheal cystitis is a condition that probably never occurs, so too are most infections of the seminal vesicles and prostate mixed. Indeed it is seldom that the gonococcus can be isolated from the vesicles either by massage or seminal vesiculotomy. On the contrary the vesicle is found to harbor a formidable array of pathogenic bacteria, among which may be named various strains of streptococci, pneumococci, staphylococci, colon bacilli, unknown Gram-negative diplococci, corynebacteria, and tubercle bacilli. Undoubtedly in many patients tagged with the diagnosis of "gonorrheal rheumatism," the gonococcus has ceased its onslaught and abandoned the trenches in the form of a chronic seminal vesiculitis, in favor of a mixed infection, of which one or more of the above-mentioned bacteria are the chief offenders. The time is ripe for the specialist as well as the general practitioner to appreciate the fact that bacterial foci, gonorrheal or non-specific, lurking often for years, in the spermatic vesicles are frequent causes for constitutional disorders in the guise of "rheumatism," articular and muscular, "rheumatoid arthritis," "arthritis deformans," "gout," hypertrophic arthritis, pains and peculiar sensations referred to the perineum, hips, thighs, back, and suprapubic regions, also a retinue of psychic disturbances as queer impulses, bordering on suicidal thoughts, panicky phobias, prone to occur on bridges, boats, trains, and in churches and theatres, dreadful dreams, loss of thought concentration, indifference to occupation and a perversion of moral character substantiating, on a pathological basis, certain tenets of the Freudian theory. To be more specific, I have frequently observed patients complaining of urinary difficulties due solely to a chronic periseminal vesiculitis and infiltration about the trigone and vesical neck, resulting in ureteral irritation and compression, and more particularly retention of urine, in one instance amounting to 15 ounces. The prevalence of epididymitis as a complication, more directly of seminal vesiculitis than of urethritis, has already been mentioned. Moreover, in this connection it should be mentioned that in the author's experience fully 50 per cent. of patients having passed through an epididymitis, exhibit a stricture of the vas deferens between the neck of the scrotum and the seminal vesicle, accounting in bilateral cases for a high percentage of sterility, not amenable to the operation of epididymovasostomy. Among other serious, if not constitutional, diseases which I have observed to be due to spermatocystitis are synovitis, arthritis, osteoperiosteitis, cystitis, pyelitis, pleurisy, endocarditis, general cutaneous eruptions, spermatorrhea, impotence, neurasthenia, and a plethora of nervous and mental conditions. Thus in comparison with diseased tonsils and pyorrhea

alveolaris, cryptic or septic infection of the seminal vesicles runs high, and I am not at all convinced that the greater evil does not rest with the vesicles. An abstract of a few case histories may be of interest:

CASE I.—P. H. B., aged forty years, had gonorrhea twenty years ago, followed by strictures, but claims he was all right until four years ago, when, after resumption of passage of sounds on himself, suffered an attack of urethral fever and urethral discharge lasting two or three weeks: Remissions of the discharge occurred and coincidently "rheumatism" of the hips and tremors of the thighs, associated with itching about the rectum for the past year. Patient is also troubled with some frequency of urination, and a few floating shreds are present in the urine. Sounds (Nos. 25 and 29 F.) passed easily through the posterior urethra. Rectal palpation revealed a palpable and tender right seminal vesicle, and the urine voided after massage showed an average of fourteen pus cells to the microscopic field.

Three months previously the patient had undergone a tonsillectomy, and recently an elaborate metabolic study and dietary precautions without material improvement. Under vesicular and prostatic massage with Janet irrigations and bacterin therapy, the pus cells in four weeks were reduced to five or six to the microscopic field and the tremors of the thighs had disappeared. Treatment was kept up for a few months and the patient discharged for the summer. Seen one year after his first visit he stated that, aside from a slight attack of "rheumatism" about six weeks after undertaking treatment, he had been free of attacks, with one exception, that occurring during the summer while in California.

CASE II.—A. C., aged twenty-eight years, contracted gonorrhea years ago, the attack lasting eight months; second attack four years ago, complicated by a bilateral epididymitis. His chief complaints were pain in the back, described by an orthopedist as relaxed sacro-iliac joints, premature ejaculations, and pain in left testicle, for which a well-known general surgeon had performed a varicocelectomy unattended by any relief. The general practitioner referring the case had prescribed nerve sedatives and given hygienic instructions. On examination per rectum the regions of both seminal vesicles were infiltrated and presented finely nodular or irregular areas. Both regions were abnormally tender and the prostate seemed to be uninvolved. Both epididymes were enlarged and nodular. The urine showed shreds and many clumps of pus cells after spermatocystic massage. The gonococcus serological test resulted weakly positive. Treatment consisted in periodic massage, irrigations, urethral dilatation and bacterin therapy. In less than a month, in patient's own words, he felt "very much better," and in less than two months he was discharged, apparently cured.

CASE III.—W. A., Jr., aged thirty years, in the course of a posterior gonorrheal urethritis, on the twentieth day of his illness, developed cystitis and a left-sided spermatocystitis and epididymitis: on the twenty-sixth day pleurisy, and on the twenty-eighth day a ureteropyelitis of the corresponding side. On the same day the patient received 4 c.c. of antigonococcic serum. Next day the urine was much clearer and the following day the patient felt much better, although pleuritic friction rub was still audible. Three days after the first injection he received a second dose of antitoxin. Two days later temperature, pulse, and respiration were normal and all signs of the more serious complications had disappeared. Eighteen days later local urethral treatment in the form of massage and irrigations could be resumed and eighteen days subsequently not a shred or pus cell could be found in the morning urine.

CASE IV.—C. J., aged twenty-eight years, came to the hospital, complaining of impotence. History elicited the facts that he had passed through three attacks of gonorrhea, once complicated with bubo. He had marked frequency of urination, rising six or eight times at night. The patient called attention to vague pains, loss of weight and vigor, disability from work, and nervousness to the point of tremors. Per rectum, both seminal vesicles were palpable and doughy and the prostate slightly boggy, especially on the right side, where it was subsequently discovered that he had a stricture of the vas deferens. The gonococcus serological test was weakly positive and the Wassermann negative. Vasopuncture for medication of the seminal vesicles, followed by sounds, irrigations, and a tonic for six months restored his pus tubes apparently to a normal condition, and at least rendered him potent sexually.

CASE V.—F. R., aged forty years, contracted gonorrhea for the first time sixteen years previously; was reinfected four years later, developed a prostatic abscess six years thereafter, and has had repeated attacks of epididymitis on both sides. One year ago the patient developed heart trouble and at present is practically bedridden with a recurrent attack of epididymitis of ten days' duration. On examination the right epididymis was found enlarged and subacutely tender; the left nodular but not tender. Per rectum the prostate and seminal vesicles on both sides were a mass of chronically inflamed and tender tissue. The urine was cloudy and full of shreds and pus. The heart was markedly dilated and associated with valvular disease and insufficiency. Blood-pressure averaged 230 (systolic). Wassermann was negative, but gonococcus serological test resulted medium positive. Treatment consisted, on the subsidence of the epididymitis, of massage and Janet irrigations, supplemented with an alternation of gonococcic and autogenous bacterins. For a time the patient showed some improvement, and he has been reported (a year later) to be still alive.

CASE VI.—J. McC., aged thirty-five years, acknowledged gonorrhea seven years before. At the time of his visit to the hospital he complained of pain in the left ankle and heel, also the right foot. Examination revealed a chronic prostatitis and a palpable and tender left seminal vesicle. Urine showed few shreds, but massage and microscopic examination of the subsequently voided urine demonstrated twenty pus cells to the one-sixth objective field. Wassermann and gonococcus serological tests were negative. Under massage, irrigations, and bacterin therapy in less than two weeks the left foot showed improvement and he was much better generally. This patient has been under treatment less than two months, and although he is not yet well, he is greatly improved in every respect. The prostate and vesicles appear normal on palpation and the urine is perfectly clear.

CASE VII.—A. L., aged fifty-five years, father of two healthy children. His chief complaints are dragging pains in both groins, lack of vigor physically and mentally, dark rings under eyes without cause, and a urethral discharge. Admitted having had gonorrhea thirty-five years ago and was treated four or five weeks. Patient stated that discharge appeared three months ago, associated with severe sharp pains in rectum; dragging pains in groins occurred only two weeks ago. He has no frequency of urination, but decided urgency. On rectal palpation, the prostate was not found to be enlarged, but considerable infiltration and induration of tissues in region of seminal vesicles and neck of bladder were demonstrable; moreover, microscopic examination of the urine after massage showed an average of twelve pus cells and many clumps of pus to the one-sixth objective field. Urethral examination revealed a chronic posterior urethritis and 15 ounces of residual urine. The Wassermann was negative, but the gonococcus serological test was weakly positive. This case is obviously one of retention of urine due to urinary obstruction on account of a seminal perivesiculitis and pericystitis. The usual treatment directed to the seminal vesicles and posterior urethra has already resulted in considerable improvement, although the case was seen only ten days ago.

CASE VIII.—H. S., aged twenty-seven years, admitted gonorrhea for the first time five years ago, with two recurrences since, the present attack being of two months' duration. A slight mucopurulent discharge was present at the external urinary meatus. The urine was full of shreds and rectal examination demonstrated a prostate normal by palpation, although subsequently a stricture of large size was found in the posterior urethra. Although the patient received no drug other than salol, ten days after his first visit, he called my attention to a punctate, papular eruption on the arms, which in the course of two weeks developed into a general papulosquamous roseola, which after negative Wassermann and positive gonococcus serological tests was diagnosed as a *gonorrheal*

roseola (Fig. 1). This opinion was concurred in by Dr. Jay F. Schamberg. The administration of antigonococcic serum on three occasions in the course of eight days, possessed an immediate and specific effect and the eruption had completely disappeared by the end of two weeks. At this time also the gonococcus serological test became negative. Subsequent treatment for a few weeks was devoted to the stricture and chronic posterior urethritis.

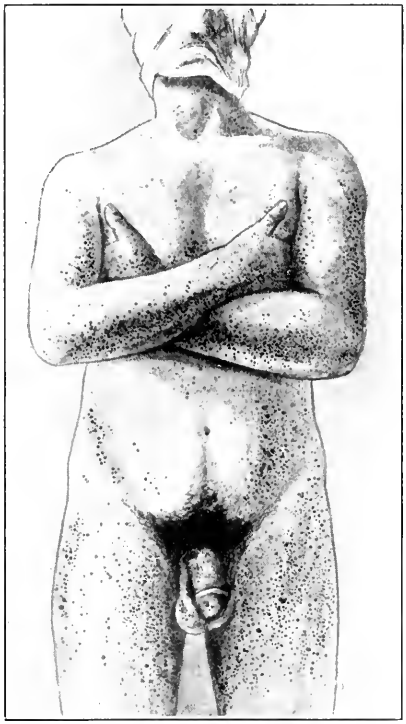
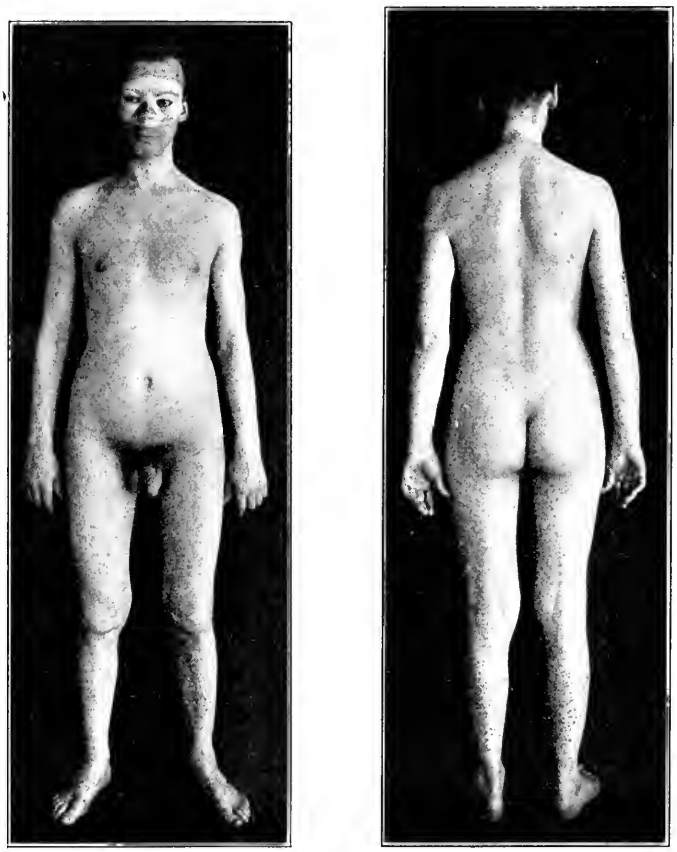


FIG. 1.—H. S. Gonorrheal roseola of two weeks' duration. (Photograph of colored drawing.) See Case VIII.

CASE IX.—E. I. B., aged thirty-five years, was referred to me with a "rash all over the body," of three weeks' duration, with the history that he had three small chancres seven years previously, when he had his first attack of gonorrhea. He admitted four attacks of urethritis, the last two months ago or five weeks prior to the present cutaneous eruption. Temperature and pulse were normal. The epithrochlear lymph nodes were palpable, but the postcervical were not. The entire body, excepting face and palms, were covered with pin-point to 2 mm.-sized, punctate, bright red papules, each with definite infiltration (Fig. 2). The urine was cloudy and contained many heavy shreds. Per rectum the prostate

felt normal, but both seminal vesicles were enlarged, hard, and unduly sensitive. The Wassermann was negative, but the gonococcus serological test resulted weakly positive. No subsidence was noted in roseola for two weeks under the usual treatment, including gonococcic bacterin, when bilateral vasopuncture was performed and both seminal vesicles medicated with a 10 per cent. solution of collargol. Ten days later the eruption was scarcely



Front view. Back view.

FIG. 2.—E. I. B. Gonorrheal roseola of three weeks' duration. See Case IX.

visible. Although from this time on, the patient never exhibited a return of further constitutional trouble, in view of a persistent nodule in left vesicle and an excess of pus in his urine after massage, he has been advised to have a repetition of vasopuncture or seminal vesiculotomy or vesiculectomy.

The medical profession owes a debt of gratitude to Jordan Lloyd of Birmingham, England, for his pioneer work as far back as

1888 in directing attention to the importance of spermatocystitis, the significance of its pathology and symptomatology and the demonstration of an operative procedure of merit, also to Fuller and Belfield in this country, for popularizing the operative treatment of this obdurate disease.

It is undoubtedly true that the vast majority of patients who fall victims of gonorrhea, complicated by seminal vesiculitis and prostatis, sustain what is commonly known as the catarrhal form, and the inflammation, after running its usual course, ends in resolution. Again in those men suffering from a more deeply seated form of the disease, proper massage and total irrigations suffice in most cases to effect a satisfactory cure. Thus operation should be considered only after massage has failed and since the particular operative procedure to be adopted depends upon the morbid process present in the vesicle, vas or ejaculatory duct, it behooves the surgeon to ascertain the nature and extent of the pathological lesions present. This knowledge may be acquired by rectal palpation, massage, microscopic examination of the expressed vesicular content, bacteriological examination, needle puncture of the vas in an attempt to detect strictures by the injection of solutions of sterile water and methylene blue and occasionally by roentgenography of the vesicles. Dependent upon the information obtained, massage and irrigations with or without bacterin therapy, vasopuncture, and spermatocystitic medication, repeated if necessary, vesiculotomy and vesiculectomy must be done in indicated cases, if we hope to eradicate this intractable disease and avoid, in many cases, systemic invasion.

HEAD COLDS FROM THE STANDPOINT OF THE INTERNIST: THEIR RESULTS AND TREATMENT.

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Head cold, variously denominated coryza, catarrh, la grippe, etc., is such a common complaint in this latitude that one is almost disposed to think of it as a necessary evil. How few ever consult a physician for this ailment. Yet unquestionably it is the cause of a vast monetary loss as well as an inestimable amount of suffering and pain. In 1911 the Boston Board of Commerce instituted an inquiry into the economic loss of colds, both as to time and money, and the results are rather startling. It was found that one-half of the population of Boston suffer from a cold during six months of the year. One-fifth of the population are absent from work all of the time as a result.

Among six hundred employees of large concerns, such as department stores, there was an average of six days' absence from work in six months as a result of colds, making an economic loss of $21 apiece, exclusive of medical attention. In addition there was a loss of energy amounting usually to $3 apiece, making a $1200 loss. Those from thirty to forty years of age, the most valuable period of life, were the worst sufferers.

By head cold, of course, I do not mean epidemic influenza—real la grippe, with Pfeiffer bacillus—that is an entirely different disease, and I hope that no one will understand that I am discussing it.

As to the cause of most if not all of these colds I think there can be but one answer, and that is that they are infections. When one in a family contracts such an attack, then practically every other member of that household, as well as most of those who come in contact with them, will be affected within a short period. Whether the cause be a coccus or an unfilterable virus, as some think, cannot as yet be determined, but the evidence is overwhelmingly in favor of infection. It is true that draughts, congestion, etc., favor the entrance or at least prepare the soil for the invader, probably already there awaiting for a suitable culture media. That there are certain cases associated with food allergies, such as those following ingestion of eggs, meat, etc., there is not much doubt, but they are in the minority. People of a gouty taint probably acquire them in this manner. Some individuals who have these colds frequently have a chronic sinus that infects the nares at stated intervals, but the majority are contact cases.

In this connection it might be well to state that three years ago, at the suggestion of Dr. Luckett, attending surgeon at the Harlem Hospital, I investigated a series of postoperative pneumonias occurring in the hospital. I found that in every instance the anesthetist or attending nurse—generally the anesthetist—was suffering from an infectious rhinitis, usually of the second type described below. Cultures in a few instances showed pneumococci, but nothing definite was ascertained by culture methods. I have since seen several cases of postoperative pneumonia, and in almost every instance have been able to establish that the anesthetist suffered from a severe head cold. I find that for years the fact has been observed that postoperative pneumonias occur very frequently in groups, which have been charged up to cone infections, etc., but I do not know if anyone has accused the anesthetist before.

In the diagnosis it may be argued that bacteriological examination should be made in each case, inasmuch as there is no agreement as to the exact causative agent, such work would be futile in practice at the present time. Clinically, the vast majority of the cases fall in a few groups, the general character of each being the same but modified by the peculiarity of the individual. At one season one group will prevail, and at another season there will be another picture.

Undoubtedly, there is a definite bacteriological basis for this grouping, but until the matter of origin is settled one must be content to follow a clinical classification.

For purposes of general discussion one may divide these colds into three classes: (1) mild; (2) moderate; (3) descending.

1. *Mild*, with little or no discomfort, limited to the nasal mucous membrane and associated with a watery discharge and slight headache for part of a day, followed by slight mucopurulent discharge; very often this slight discharge is associated with a few drops of blood. After the second or third day the discomfort is scarcely noticeable, and if questioned a week or so later the patient must plainly make an effort to recall the cold and the bleeding. In a fair proportion of these cases, somewhere between the fourth to the eighth day, there develops an attack of muscular pain and soreness —a variously denominated lumbago, stiff neck, pleurodynia, or muscular rheumatism—and, curiously enough, the patient states that he thinks he has taken cold, although apparently he never associates the head cold and the muscular pain. This is somewhat analogous to the nephritis developing three or four weeks after the onset of scarlet fever. In some instances the pain is spontaneous; in others the myositis seems to be present only when the patient makes some sudden effort, as in stooping, etc. These pains persist for a varying period—usually two to five days or more—and then generally, but by no means always, disappear. The head colds contracted in the spring seem to be more commonly followed by these symptoms than those occurring in winter. This pain is evidently due to a toxemia resulting from the nasal infection. After many inquiries I have yet to see an attack of rheumatic fever follow such a cold. Possibly the infecting agent is not sufficiently virulent.

The relation which these backaches and so-called muscular pains bear to nose cold must have been observed an innumerable number of times, yet I am not cognizant that this fact has been pointed out in the literature. It is true that Rosenow believes that he has discovered cocci in the muscles in cases of lumbago, etc., consequent to disease of teeth and tonsils, but I do not find anyone who has done so after a rhinitis and yet there is no reason why they should not be present after such infection. The ache, when it does occur, is evident in nearly every instance before the eighth day from the appearance of the first symptom. Of course, there are plenty of such colds that are never followed by painful attacks, but aside from those aches manifestly due to mechanical causes and gaseous distention, most of the so-called muscular rheumatism will be found to follow within a week or two of a head cold. The chronic cases are doubtless connected with old sinus infections.

Sometimes nerves, such as the sciatic or brachial, are affected, and a true neuritis follows. Since I have thought along these lines, it appears that most of the hitherto unexplained cases of sciatic

and brachial neuritis occurring in hospital practice have followed within a week or so after a catarrhal cold. In two instances, treatment directed to the nasal infection brought about cure after other measures had been absolutely unavailing. It is not intended to maintain that all forms of brachial and sciatic neuritis are due to head colds, but they are at least a frequent cause. In a few cases I have been able to associate a similar relation of cause and effect between the onset of head cold and a phlebitis occurring in the varicose veins of the leg. Whether or not this was only a coincidence, the number of cases has been too small to determine definitely.

2. *The moderately severe cases* begin in the same way as the mild cases, but in a day or two the discharge becomes muco-purulent, and later purulent, often excoriating the skin and mucous membrane; there is loss of the sense of taste and smell, and sometimes marked sinus or middle ear involvement. In the first day or two of these cases, there is usually some muscular soreness and pain, but it is general in character and passes off by the third day. It is not common to find it appearing after the fourth day, as in the mild cases above mentioned, although sometimes it does occur and then it is apt to be very persistent. The total duration of the average case in this group is from ten to twelve days.

3. *The third or descending group* begins as the last-named type, but steadily invades the other tissues farther down: (1) the throat and pharynx, as evidenced by pain and soreness in swallowing, and (2) by the third or fourth day the bronchi are invaded and there is well-marked cough and expectoration. In some individuals this sequence follows every head cold no matter how mild it may be. Most if not all the office cases of bronchitis that one ordinarily sees through the winter season come with just such a history. The symptoms and clinical course of such attacks are so well known that a further description is unnecessary, and it is only mentioned here because it is part and parcel of the head cold, and to point out that its rapid cure depends on treating the original focus of infection in the head.

As has been stated, the average patient rarely consults a physician for a head cold (1) because he has been told so frequently by physicians themselves, or by the altruistic paper-writing physician of the daily press, that there is no cure for this affection; or if he does perchance go to a physician he is usually dismissed with a prescription for some capsules which, on reading, he finds contain phenacetin and aspirin, and he is advised to take quinine or a Dover's powder at bedtime. As a consequence of this advice he does not see much difference in the duration or severity of the attack as treated in this way and when treated according to his own custom, so he does not try again.

Now, while it is true that, excepting those who claim such marvelous results from specific vaccines, there is no one who can claim

a cure for a head cold in the sense of a specific, yet it were just as logical to say that because we have no specific for pneumonia, typhoid fever, etc., that we cannot do anything for them. We can at least lessen symptoms, prevent complications, and hasten recovery. All of these things we can do for head colds, and it is of just as much importance to treat them as the infections mentioned above, because they are of more importance in the aggregate, both as to number and complications, than any other single infection, be it typhoid fever or tuberculosis. This may seem a startling statement, but if one considers their great frequency, the complications—the otitis, mastoiditis, and other sinus involvement—and the disability as already mentioned it will not appear to be an exaggeration.

TREATMENT. There is no sound basis for believing that any of these colds may be aborted, although many have fond delusions of so doing.

Before discussing the special methods of treating it seems proper to discuss the general hygienic measures.

When the patient comes on the first day of the disease the diet should be restricted, *i. e.*, he should strive to get up from the table hungry. Curiously enough, at the commencement of these colds many people have a prodigious appetite. Partaking of large quantities of protein food unquestionably increases the nasal congestion. Purgation early and often should be practised during the first few days, as by its derivative effect the turgescence of the turbinates is markedly lessened, and for that reason the headaches are usually much relieved on free purgation.

Most physicians prescribe one cathartic at the commencement, but it should be repeated on alternate days in cases that do not clear up promptly. A hot mustard foot bath also acts as a derivative, and is particularly valuable on the first and second day of the cold.

The stereotyped advice should always be given to avoid draughts, wet feet, and crowded places. Many a pneumonia has followed in the wake of a coryza after the patient has returned from a theater or other crowded place.

Tobacco must be interdicted for a few days at least. Alcohol in the form of beer, whisky, or rum is absolutely contra-indicated. The old notion that hot toddy helped a cold is due to the fact that the patient forgot his aches and troubles more quickly under the narcotic influence. The sweat and few extra hours in bed undoubtedly make the patient feel better and hasten recovery, but any other diaphoretic agent would do the same, and do it more safely. A hot lemonade is quite as efficacious.

In all disease of the mucous membranes it is a well-known fact that nothing so much impedes recovery as the taking of even small quantities of beer or whisky, and this should be particularly impressed on the patient when such cases do not readily respond to treatment.

Quinin. I suppose that two-thirds of the profession prescribe quinin in the early stages of these complaints, and some continue its use throughout. Certainly, there is no agent which so quickly congests the mucous membranes of the tract as quinin, and sometimes even in small doses. One can understand the homeopath prescribing small doses of quinin on the Hahnemannian principle that slight congestion will relieve intense congestion, but from any other view-point it is difficult to see the *rationale* of its action. There are millions who swear by it, as I suppose there were millions who vouched for the value of blood-letting, antimony, etc. Personally, I have never seen any good from its use, although I have used it often and in various doses; and I have often seen harm follow its use.

Dover's powder is still used at the onset, oftentimes with the idea of aborting the cold. Unfortunately, medicines can rarely strangle germs. It is not as popular as it used to be, possibly because more people now seem to be susceptible to the disagreeable after effects of opium than formerly, or because of the anti-opium hysteria which has spread over the country. I have never satisfied myself that its benefits equalled its disadvantages.

Acetyl acid salicylic, I believe, does relieve symptoms, and in small doses it does not congest the mucous membrane seriously. In some patients relief is undoubtedly afforded by atropin. Under the title of rhinitis tablets this medication is much in vogue. The well-known combination of quinin sulphate ($\frac{1}{2}$ grain), fluidextract of belladonna ($\frac{1}{8}$ grain), camphor ($\frac{1}{4}$ grain) makes the practitioner feel that he is orthodox in using quinin and camphor in treating a cold; but it is the atropin that produces the results. The dryness of the mucous membrane that follows its use causes most people, after a time, to discontinue it. In order to obtain good results it must be given early in the attack, *i. e.*, within the first twelve hours, and repeated every half hour or so until the physiological effect is produced. Of course, it does not cure the cold, but it alleviates the most prominent symptoms of coryza during the first day or two. After that the disease runs as before. It is useless in the moderate and descending types of the disease. When the profuse watery discharge is very troublesome a powder consisting of bismuth subnitrate (dr. ij), starch (dr. j), gum arabic (dr. ss), with menthol (gr. ij) or antipyrin (gr. x), may be snuffed up. This almost always gives considerable relief.

Much has been said of the use of vaccines in this complaint, but it is difficult to judge of their effect because the vast majority of the cases are in the very nature of things better before a second injection may be made. If one takes the standard laid down by Wright and his followers, who state that there is no marked improvement in the opsonic index in the vaccinated before a period of from four to seven days afterthe first injection, then by the time the second injection is

due nature has cleared up most of these cases so that it is difficult to decide what effect has been produced. Whether their continued use at the approach of the fall and winter season will prevent subsequent attacks is also a matter that must always be open to question, as nature sometimes herself protects. Personally, my results with vaccines, either as a curative or a prophylactic measure, have not been successful.

Practically all of those who consult a physician for this complaint do not do so until after the second day of its invasion. At this time, again, the hygienic advice mentioned above should always be given. If there be much general soreness or pain, acetphenetiden may be added to the acetyl acid salicylic, but the atropin is useless. However, in these cases the local treatment is by far the most important. It has been my habit to begin with an alkaline spray under fifteen to twenty pounds air pressure. This is always followed by a free exudation of mucus. This is repeated until a mild blowing of the nose is not followed by mucopus.

In very sensitive nostrils a spray of 0.5 per cent. cocain may be employed previously, but I have rarely found it necessary. If there be much headache or face pain an adrenalin spray of $\frac{1}{10000}$ is employed; usually this is not necessary. Ordinarily after the alkaline spray the following spray is used: Acid. carbolic., ℥iij; iodin, kalii iodid., āā gr. vj; aqua menth., glycerin., āā ℥ss; aq., q.s. ad ℥iij. This is sprayed until it reaches the throat.

After this an oil spray is employed for about two minutes. The composition of this oil spray is as follows: Ol. cloves, ℥x; camphomenthol, gr. xxiv; ol. pinus sylvestris, ℥xx; liq. petrolatum, q.s. ad ℥iij.

All of this treatment does not consume more than five minutes when an electric power pump is used.

By these measures one does not intend to destroy all the germs but rather to lessen their virulence and provide drainage, sound surgical measures in any infection. When the infection has traveled to the bronchi these cases are usually treated by various expectorants and narcotics.

No one can gainsay that such expectorant medicines do produce good results in the way of alleviating symptoms and hastening recovery, and they should be always employed, even though their efficiency cannot be determined or proved by animal experiments. Certain it is that if one examines the nose of the average patient who presents this sequence of coryza, tracheitis, and bronchitis he will find there is much inflammatory reaction still present in the nose several days after the nasal symptoms have subsided. In all of these cases of bronchitis, if the nose be treated in the way outlined above in addition to the internal medication by expectorants, the patient recovers in a little over one-half the time that is required when only internal medication is employed.

After a patient has been treated in the manner outlined he volubly expresses the opinion that he feels much better. His efficiency for work has increased for at least that day by about 50 per cent., in many instances by 100 per cent. If he has been accustomed to stay at home during such an attack he is almost always put in a condition to go to business, and so, economically as well as physically, he is the gainer. For this reason he is anxious to be treated daily until recovery has taken place, so that cure is really effected in the sense of freedom from symptoms and ability to do a regular day's work. Furthermore, complications and sequelæ are less likely to occur. As a proof of the efficiency, such a patient nearly always comes back for treatment.

I am perfectly well aware there is nothing original in the use of these measures; that thousands of doctors are and have been using them; but there is a tendency among internists to consider the nose as the exclusive field of the nasal specialist. One reason of this at least is the practitioner's disinclination to perform manual labor. The average internist believes that his duty ends with an examination of the patient, the writing of a prescription, and a linguistic dissertation of greater or less length. He has a horror of getting out of his chair after the examination. Too many are glued to the chair from the start to the finish of a consultation. Next to the alimentary tract the nose is the most frequent avenue of infection in the human body, and the principal evidence of such infection is the symptom coryza. It is just as much the field of the internist to treat such symptoms by local applications as it is to wash out the stomach when necessary for gastric complaints.

Finally, for purposes of discussion, I would like to emphaisze the following conclusions:

1. That there is a special type of head cold that precedes by from four to eight days most, if not all, cases of so-called muscular rheumatism, lumbago, etc., and that this is more satisfactorily treated by treating the original site of infection in the nose than by the usual methods of treatment.

2. That bronchitis following such head colds is likewise more satisfactorily treated by taking care of the original source of infection in the nose.

3. That this field of nasal treatment is quite as much the province of the internist as the use of the stomach pump in gastric lavage.

4. That a fair proportion of postoperative pneumonias is due to infection of the patient by the anesthetist who is suffering from a severe head cold himself.

THE DIAGNOSIS OF MELANOMA (MELANOTIC SARCOMA) BY MEANS OF THE RESULTANT EFFUSIONS.

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Melanoma, though not a rarity, is a malady of more than passing interest, both clinically and pathologically, and the diagnosis, by no means difficult histologically, is not always recognized without surgical intervention during life. Any method, therefore, which throws light upon its presence without the necessity of an otherwise advisable exploratory operation saves the patient a needless ordeal and is a welcome aid to the internist.

The laboratory findings of the effusions obtained by paracentesis for therapeutic purposes in the two following cases were most significant. In the event that effusions into the pleural and peritoneal sacs as a result of this malady are as frequent as these experiences would indicate, rather than the anomaly that the paucity or absence of references in the literature would suggest, it seems doubly advisable to make note of the results obtained.

The fluid derived from the thorax of Case I was referred to the laboratory of Dr. Charles E. Simon by Dr. R. B. Morris in February, 1915. Dr. Simon has allowed me to report on these findings. The history of the case was obtained through the courtesy of Dr. O. F. Kunkle, and for the gross autopsy findings I am indebted to Dr. Morris, both of Olean, New York. Case II was admitted to the medical division of Mercy Hospital in the service of Dr. Wm. F. Lockwood, to whom I am likewise indebted for permission to report the case. This patient, relieved of his complaint, insisted upon leaving the hospital after a period of a few days, but in conjunction with the findings of the previous proved case the diagnosis of melanoma seems fully warranted.

The fluids in both cases were obtained at times in the clinical course of the disease when there was absence of the usual diagnostic signs, *e. g.*, melanuria, characteristic pigmentation of the skin, or suspicious tumor of the skin or choroid.

Macroscopically the fluids were almost identical in appearance. When agitated they were quite opaque, even in relatively thin layers when viewed by transmitted light. On sedimentating there was a dense dark brick-dust layer at the bottom, while the supernatant fluid, though intensely pigmented, was clear and appeared dark reddish brown in color. The surface layer was slightly iridescent, with a predominant greenish tone. The foam, obtained by shaking, had a tendency to a pinkish hue in Case I and a dirty olive green in

Case II. When the light fell directly upon the fluids in both thick and relatively thin layers it was almost black so intense was the pigmentation. Here too a slight difference was noted, Case I being of a slightly reddish and Case II of a greenish tinge. They appear not unlike crude petroleum with their deceptive play of iridescent colors. In very thin layers viewed by direct light the fluids were reddish to greenish yellow.

The supernatant fluid when tested with a strong solution of ferric chloride showed no reaction for melanogen, but on the addition of bromine water a yellow cheesy precipitate was formed which became much darker on standing, finally becoming almost black, thus indicating that the transformation from melanogen to melanin had been complete *in vivo*. Tests for bile pigments were negative.

Microscopically the sediment showed not only red blood corpuscles, epithelial cells, and numerous leukocytes, but also many tumor cells, which when unstained had the typical pigmented granules of melanoma. These cells were round or oval for the most part, occasionally polygonal; the round or oval nucleus was usually centrally placed, frequently showed mitosis, and occasionally was extruded from the cell; often the nucleus was completely hidden by the closely packed brown granules included in the cytoplasm of the cell; the granules themselves were coarse, irregular in size and shape, and of an intense brown color. When stained the entire cell was basophilic, the granules intensely so. The separate granules were apparently bound together by a delicate basophilic reticulum.

The specific gravity of the fluids varied between 10.24 and 1.030.

Case I.—K. B., a spinster, aged forty years, a saleswoman by occupation, complained of spitting of blood which began about May 1, 1914.

Family history was free from tuberculous taint, but her maternal grandmother and one maternal aunt died of cancer.

Past history revealed that she had never been robust. She had had the usual diseases of childhood. In 1906 she had what she considered a severe cold, which lasted about two years. After recovery from this she was better than ever before, until October, 1913, she began feeling tired, had no energy, and was bothered considerably with dyspepsia. There was, however, another period of good health which continued up to the onset of the present illness.

Present Illness. This began May 1, 1914, with loss of weight, apetite, and energy, soon followed by hemoptysis. After the initial hemoptysis there was daily expectoration of sputum streaked with blood.

Physical examination made May 15, 1914, was unimportant, save for the chest. Here there was indefinite impairment of resonance at both apices, slight prolongation of expiration above the clavicles, slight interrupted breathing at the apex of the left lung, numerous fine rales elicited only after cough above the second rib on both

fronts and above the spine of the scapula on the left and a little lower than this on the right behind, and finally an "abnormal" transmission of whispered voice sounds over the dorsal vertebræ.

On these physical findings, together with the history, a diagnosis of early tuberculosis was made involving the apices of both lungs and the mediastinal glands.

Course of the Disease. The patient was admitted to a sanatorium June 20, 1914. Her temperature seemed to corroborate the diagnosis of tuberculosis. She improved in every way, with the single exception that she continued to expectorate sputum streaked with blood for a period of eight months subsequent to her admission, despite the usual measures employed for its control. Tuberculin (form not stated) was given in very small doses, with only ephemeral improvement. During these eight months the adventitious sounds in the chest largely disappeared, the rales being practically confined to the apex of the right lung. The sputum was repeatedly examined but never showed any tubercle bacilli, neither were any cells found to suggest malignant disease. December, 1914, a roentgen-ray plate made by Dr. Morris showed slight clouding of the apices. The descending arch of the aorta showed a conspicuous shadow and the mediastinal shadow was slightly broadened. From the root of the left lung, extending downward and blending intimately with the shadow of the heart, was an intense clouding, showing areas through which the light was more readily transmitted. At this time (December 7) hemoglobin was 68 per cent., red cells 6,312,000(?), leukocytes 9200. A differential count was not made. The apices at this time were practically clear, but careful examination over the area corresponding to the shadow of the roentgen-ray plate showed slighty impaired resonance and a few rales. At this time (seven and a half months after the onset of her illness) the patient had gained eight pounds and was a little heavier than her usual weight when in good health. January 6, 1915, the patient felt a slight pain on the left side and a few days later she felt a gurgle within the chest. The day after she experienced some dyspnea. Ten days after the onset of this train of symptoms she showed dulness at the left base with Skodaic resonance above. A spontaneous hydropneumothorax was diagnosed which was confirmed by roentgen ray. Exploratory puncture showed the effusion to be "bloody." Three laboratories reported the fluid to be sterile, without tubercle bacilli and with an absence of malignant cells. Guinea-pigs six weeks after inoculation showed no evidence of disease at autopsy. The cytological examination was essentially that of normal blood. Following the development of the hemopneumothorax, cough, expectoration, and hemoptysis ceased. February 13 paracentesis was done for the relief of pressure symptoms. The pleura at the sixth interspace in the midaxillary line was markedly resistant to the introduction of the needle. Twenty-four ounces of coffee-colored fluid were removed. Subsequently the

rapid reaccumulation of the same character of fluid necessitated aspiration at about five-day intervals. The fluid obtained February 24 was the first which reached us, and has been previously described. A definite diagnosis of melanoma was made at this time. At the site of the puncture of February 13 a metastatic pigmented growth developed within a few weeks. The day following this aspiration the patient developed a fever which continued until the end. The decline from this time was rapid. The patient died April 6, 1915.

Pathological Findings. Autopsy performed the day of death by Dr. Morris showed the following points of interest: The left pleural cavity contained a large quantity of bloody fluid, the left lung being compressed into a small space. The right lung was likewise partially compressed. There was no gross lesion suggesting tuberculosis. The heart was completely displaced to the right. Careful examination of the abdominal organs for the primary growth revealed nothing. Save for a general enteroptosis all of the organs were normal. The uterus was infantile and contained a single subserous nodule. The retroperitoneal and mesenteric glands were normal. There was no note of any pigmented moles or of the condition of the eye-grounds. The thoracic viscera together with the uterus were sent to Dr. Simon for examination. The uterine nodule on histological section was a fibromyoma. The hylus of the left lung was almost replaced by a friable, partially necrotic, brown mass invading the parenchyma of the left lung and the visceral pleura. At this point there was direct communication between the pleural cavity and the bronchial tree. The extent of this mass was considerable, involving the major portion of the collapsed left lung. Histological section showed the typical structure and pigmented cells of melanoma.

Case II.—W. C. P., aged thirty-four years; driver by occupation; admitted to the Mercy Hospital April 5, 1916, complaining of swelling of the abdomen.

Family History. Mother and one maternal uncle died of tuberculosis many years ago. There was no history of malignancy. One child died shortly after birth. It had a spina bifida. Otherwise the family history was without interest.

Personal History. Patient's health has always been good. Save for measles and mumps during childhood he has never had any illness. His habits were bad. He smoked from twenty-five to thirty cigarettes a day and for many years he has drunk fifteen or more glasses of beer daily. In addition he has occasionally gone on a spree, when whisky and gin were taken. His occupation exposes him to all sorts of weather. He denied venereal infection (the Wassermann reaction was negative).

Present Illness. This began eight months before admission with gradual abdominal enlargement. For the first four months there was no pain and the patient thought he was getting fat. Four months ago he began to experience pain in the lower left quadrant,

intermittent in character and exaggerated on standing and walking or on eating or drinking. At this time the distention was as marked as on admission. He entered the hospital for an accentuation of the pain in the lower left quadrant.

Physical Examination. The patient, a marked brunette of medium build and well-nourished, showed slight dyspnea. The skin, though dark and slightly sallow, showed no jaundice or other abnormal pigmentation. The conjunctivæ and mucous membranes were of normal color. The eyes were not prominent, vision was normal and the pupils in every way normal except being slightly dilated. Pulse, respiration, and temperature were normal. The glandular system was normal. The thorax, save for the upward displacement of its viscera, was unimportant. The abdominal distention gave rise to shallow respirations, decreased vocal fremitus at the bases, with impairment of the percussion note over the same and diminished breath sounds over these regions. The P. M. I. was in the fourth interspace 1 cm. inside the nipple line and the hepatic dulness began in the fifth interspace in the right mammillary line, merging with the general abdominal dulness below. The outline of the spleen was obliterated by abdominal dulness. The abdomen was markedly distended, symmetrical, and dome-shaped. The epigastric veins were markedly distended, but there was no caput medusæ. Numerous striæ covered the entire abdomen. The distention was so great that none of the underlying organs were palpable even on dipping sharply with the palpating fingers. Dulness extended over the entire abdomen except for a small area in the lower left quadrant, where the note was tympanitic. There was no shifting in the location of dulness or tympany upon turning to either side or when the hips were elevated. Distinct fluctuation was elicited, the impulse wave being sharp, quick, and rebounding in character. The genitalia and extremities were in no way abnormal. Total red cells were 5,864,000, leukocytes 14,000, small lymphocytes 10 per cent., large monos. 12 per cent., polys. 75 per cent., and eosinophiles 3 per cent. The urine contained a trace of albumin and numerous hyaline and granular casts. There was an absence of bile. The urine did not turn dark on standing nor was melanogen or melanin present by chemical tests.

Course of the Disease. Paracentesis was performed April 9, 1916. About 3 liters of coffee-colored fluid were withdrawn. This contained numerous melanoma cells and a few eosinophiles and epithelial cells. Neutrophiles and lymphocytes were in about equal numbers. There were numerous erythrocytes present.

Two days after paracentesis the patient felt entirely relieved. Examination of the eye-grounds at this time showed the disk, vessels and maculæ normal. Through the retina the choroid showed diffusely dark, but not more so than the patient's complexion justified. No tumor was observed. The skin, uniformly dark, showed

numerous small pigmented moles of medium dark color. Over the right posterior-superior spine of the ilium was an absolutely black mole, split pea in size, slightly elevated, with the margin circumscribed and apparently not invasive. The thoracic viscera were in normal position. The abdomen, now scaphoid, had flabby walls. The note all over the abdomen was tympanitic save in the upper right quadrant, where it was quite flat and did not shift with change of position or with respiration.

Here too a small, firm, indefinite mass was felt which was apparently attached to the parietal wall. Neither kidney was felt nor was the edge of the liver palpable. The following day the patient, relieved of his discomfort, insisted upon leaving the hospital.

Conclusions. The character of the two fluids obtained from the cases here described were so nearly identical in gross appearance, chemical reactions, and the microscopic appearance of the sediments that the unconfirmed diagnosis in the second case seems hardly open to doubt.

In the two cases here diagnosed the character of the effusion was the sole clue to the nature of the malady at the time it furnished evidence of the disease.

It is reasonable to suppose that visceral melanoma is not infrequently associated with effusion, and that a study of its character will be helpful in the diagnosis of other doubtful cases.

THE EFFECT OF CASTRATION UPON OSTEOMALACIA IN THE MALE.[1]

By Charles A. Elliott, M.D.,

and

Walter H. Nadler, M.D.,

Chicago.

The case presented is of interest because osteomalacia in males is a rare condition. It is of interest also, because, while the operation has long been suggested, there is no other report, as far as we know, of a male patient treated by castration. This patient has been under observation long enough to warrant some conclusions as to the probable effect of castration.

Dock found reported in this country, up to 1895, only 11 cases of osteomalacia, all in females. Hahn, in 1899, was able to collect from the literature 42 cases in males, but the diagnosis of some of these is in doubt. McCrudden, in 1910, stated that among 360 cases of osteomalacia reported by five writers, 39 were in men.

[1] Presented to the Chicago Society of Internal Medicine, May 22, 1916.

Without making a special search he found reported in the last twenty-five years 10 cases in unmarried females and 9 cases in males. In 4 of the latter the diagnosis was confirmed by necropsy.

Case History. The patient, aged thirty-four years, first came under observation in October, 1910. At that time he complained of pain in the hips, groin, and heels.

Fig. 1.—Patient at time of first examination, October, 1910.

Fig. 2.—Five years after operation August, 1916.

In 1906 and 1907, while training for a wrestling match, he noticed a soreness across the chest and an unusual shortness of breath after running. He had previously been perfectly well. On March 17, 1907, he was thrown in a match by a scissors hold. The squeezing of his chest caused excruciating pain. In July, while working on a farm, it was remarked that the bib of his overalls seemed pushed forward. Later, he noticed stiffness and tender-

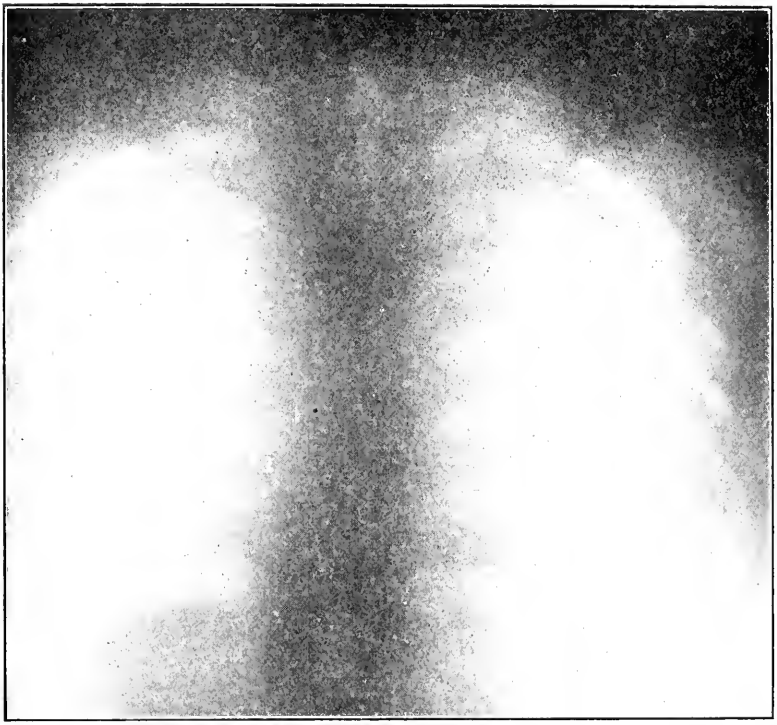

FIG. 3.—Chest radiogram, October, 1910. Note the apparently poor radiogram due to the loss of lime deposit.

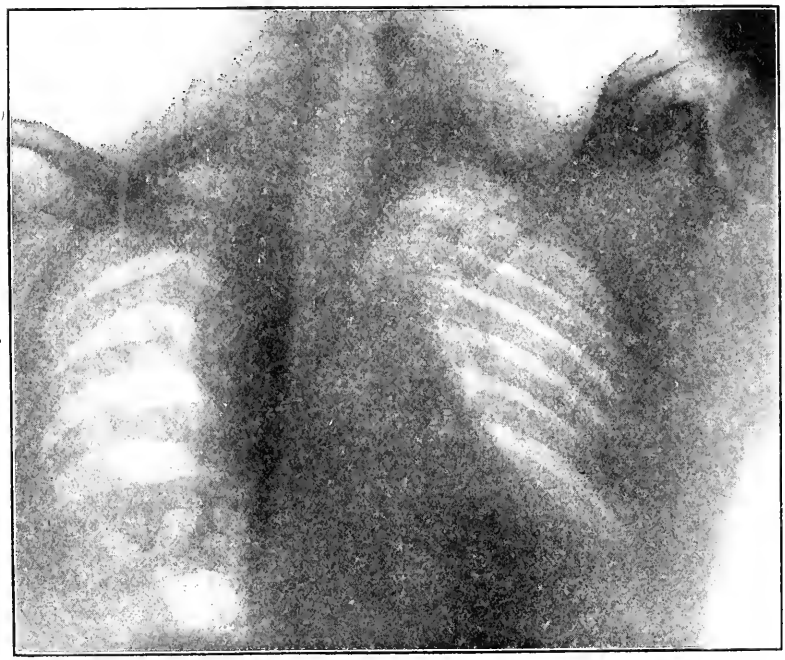

FIG. 4.—Chest radiogram, November, 1913

ness of both Achilles' tendons. In the summer of 1908 the heels felt bruised and sore. He was treated for flat-foot and rheumatism, without relief. At this time, although he seemed aware of a deformity, the chest was pronounced normal by several examiners. After seven months the knees became painful and two months later the hips were affected. There was pain in the upper thigh, especially upon rising from a sitting position. During this period the patient performed hard manual work, in the hope of regaining his health. After some months the chest became noticeably deformed. He was unable to stoop because of pain in the hips. He could not rise without the aid of his hands.

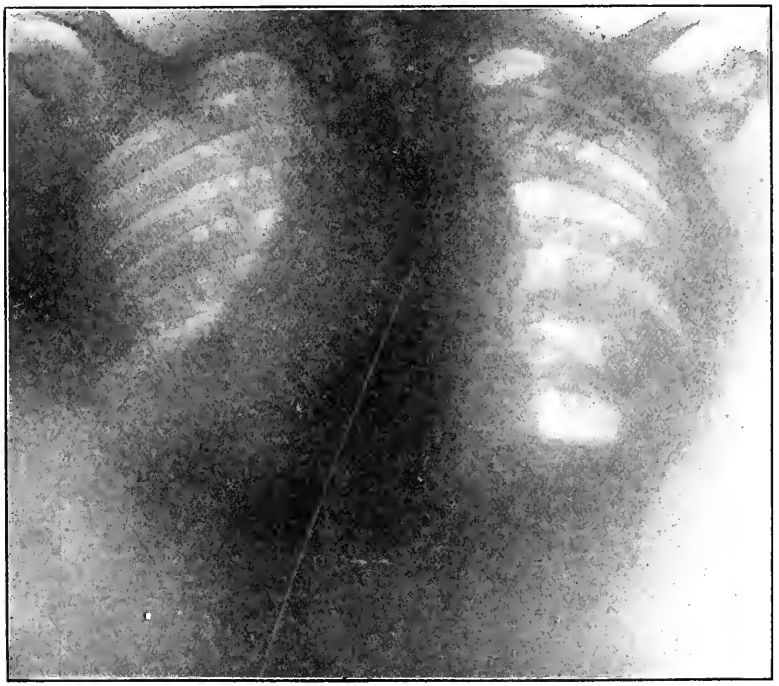

FIG. 5.—Chest radiogram, May, 1916.

There was no family history of deformity, goitre, tuberculosis, or malignancy. The patient had measles at four years, followed by whooping-cough. He had no fractured bones except a broken clavicle in infancy. He denied venereal infection. There had never been much hair upon his face or body; he needed to shave only once in two weeks.

The patient had been an athlete since the age of thirteen years. From 1904 to 1907 he was in the United States Army, chiefly as cook. He became a professional wrestler; he boxed and wrestled frequently. He could raise 500 pounds above his head. When

nineteen years he stood 5 feet $11\frac{3}{4}$ inches in his bare feet and weighed 160 pounds.

When first examined, in 1910, the patient was fairly well nourished and weighed 127 pounds. He had moderate general adenopathy. The chest showed great prominence anteriorly with lateral compression (pigeon breast). Marked angulation at the level of the sixth and seventh vertebræ. The ribs were very pliable and could be pressed back into the normal anteroposterior position.

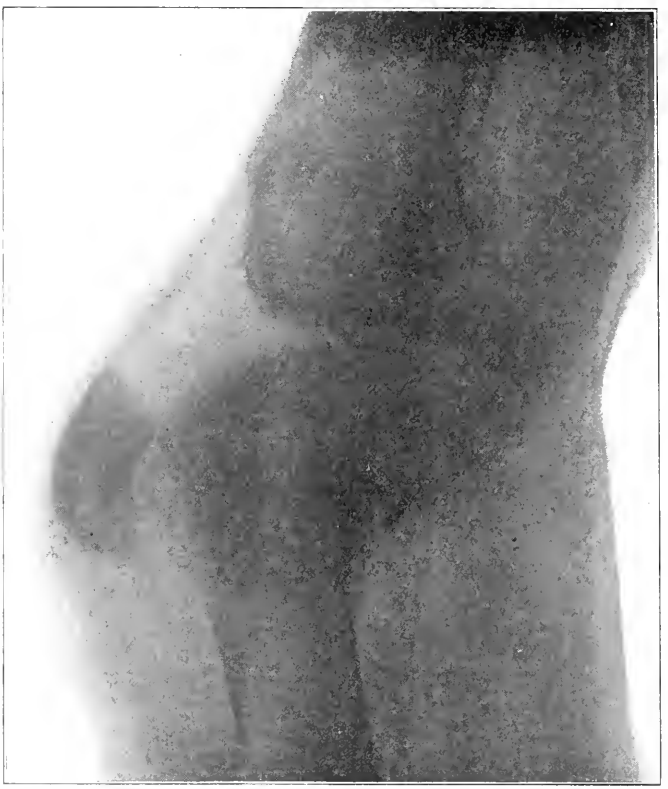

FIG. 6.—Region of the knee-joint. Radiogram of December, 1912.

The iliac bones were very tender. Intense pain was produced by pushing together the iliac crests. Both heel bones were tender.

No other abnormalities were found. Blood and urine were normal; the Wassermann test was negative. Radiograms showed a characteristic loss of bone markings and mineral deposit as well as chest deformity.

Treatment with phosphorus was begun and was followed for over three years. Thyroid extract, pituitrin, Fowler's solution, green vegetable diet, and adrenalin caused no improvement. On

the contrary the bones remained soft and tender and the chest deformity increased. In June, 1911, both testes were removed by Dr. Allen B. Kanavel. They were reported normal grossly and histologically. Examination of the urine and feces showed, contrary to expectation, an increased elimination of CaO and P_2O_5 in the days following as compared with the days immediately preceding operation.

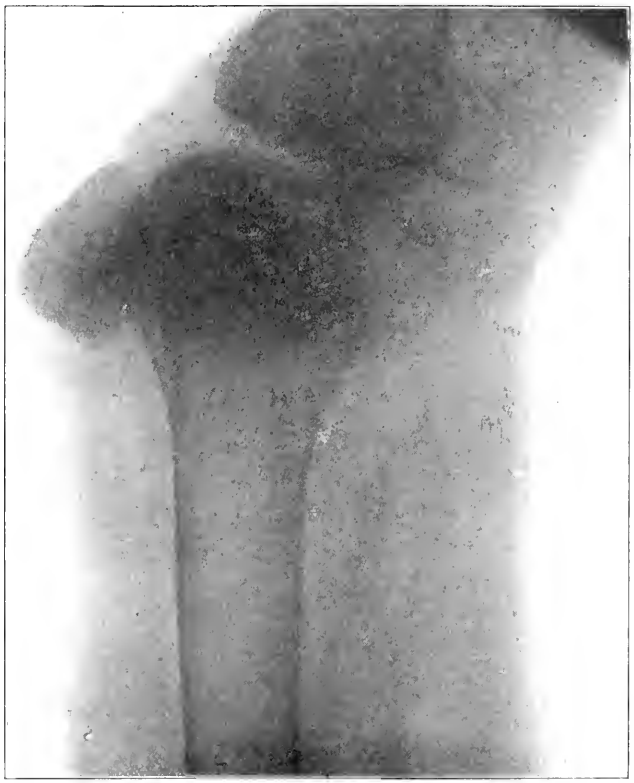

FIG. 7.—Region of the knee-joint, May, 1916.

Six months after operation the patient felt well, but the chest deformity had reached a high grade. After fourteen months, while on thyroid extract treatment, he became very nervous and developed a tremor which has persisted. There had been no tremor before this time. One year after operation the bones seemed harder. Sugar tolerance was increased, elimination following the feeding of 124 grams of glucose.

In 1913 there was less pain and the patient was able to walk five blocks without difficulty. His height was 5 feet 5 inches. He stood several inches taller in the morning than at night. Radio-

grams showed increased chest deformity and no improvement in bone structure. In 1914 nervousness and tremor increased. Since 1915, when medication was stopped, he has used a crutch and a cane for the relief of pain in walking.

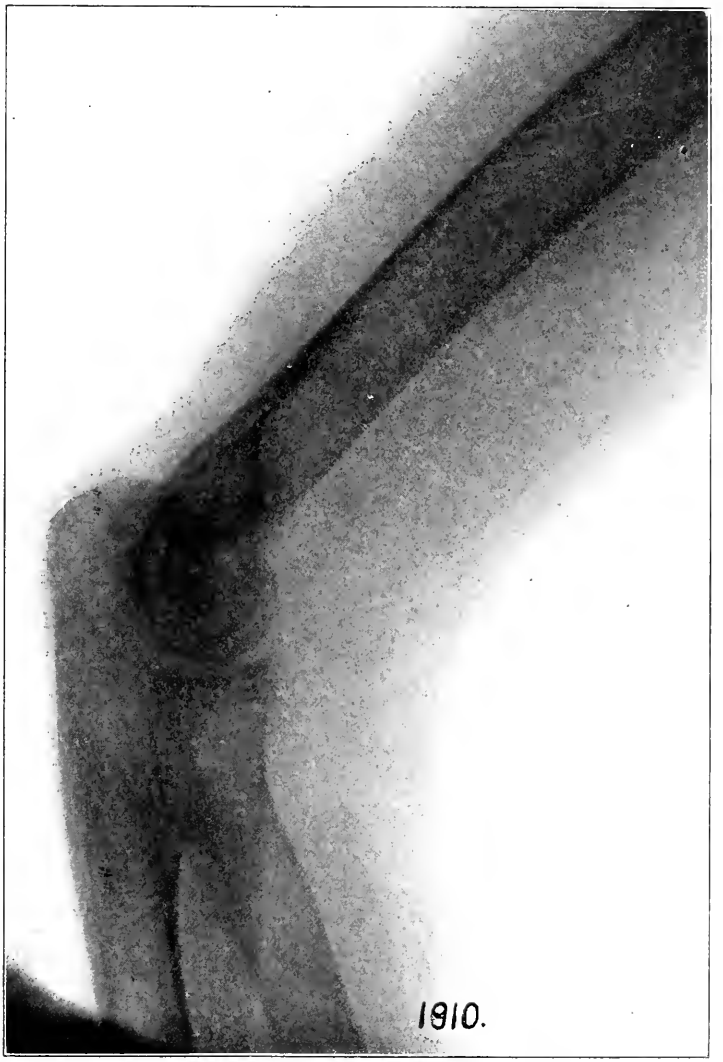

FIG. 8.—Region of the elbow-joint, October, 1910.

At the present time the patient states that he has recovered from his former "lost" feeling. He dates the improvement from six months after operation. The pain in the knees has persisted. There have been no signs or symptoms of stones in the urinary

tract. The thyroid is small; the palpebral fissures seem wide; a fine tremor is present. There is a moderate secondary anemia. Temperature has been normal throughout the course. No foci of infection have been found. While the bones seem harder, radio-

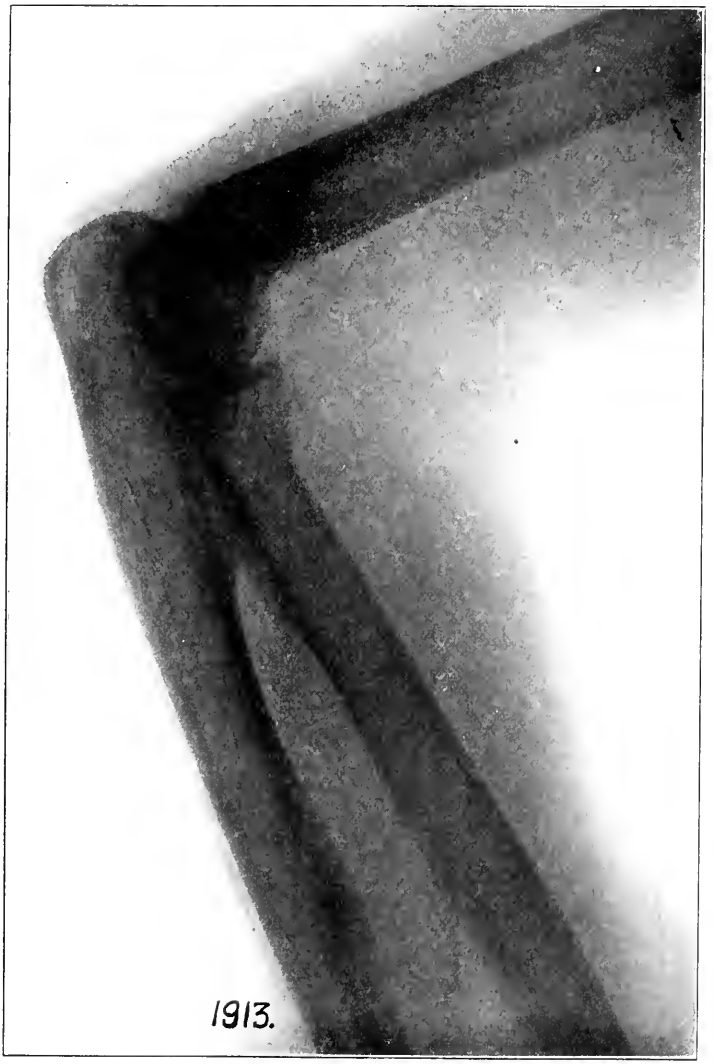

FIG. 9.—Region of the elbow-joint, November, 1913.

grams show no improvement in the general structure but rather an increased porosity. The skull bones participate in the loss of mineral deposit; the sella turcica is small.

The case presented is one of osteomalacia of the type designated

metaplastic malacia or fibrous osteitis by von Recklinghausen, who suggests an analogy to inflammatory fibrous tissue produced in chronic myocarditis and hepatitis.

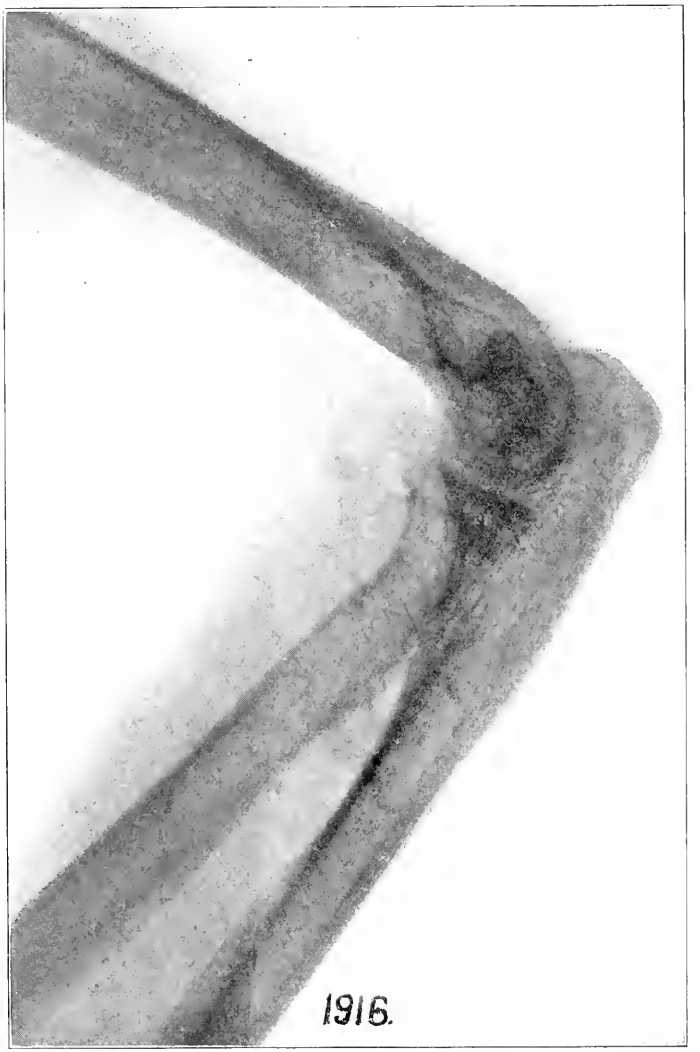

FIG. 10.—Region of the elbow-joint, May, 1916.

In this case the process seems to have begun nine to ten years ago in the vertebral column, although very early there were symptoms which led to the diagnosis of "rheumatism." The early involvement of all the bones is characteristic of male osteomalacia. As in the other cases reported there was no response to the usual methods of treatment.

A possible etiological factor in this case was the injury to bones incurred in boxing and wrestling. Such injuries, not severe enough to cause fractures, may, according to McCrudden, be sufficient to upset the balance of bone metabolism. There has been no evidence of disturbed internal secretion beyond increased sugar tolerance and rapid development of a persistent tremor after a short course of thyroid extract.

In spite of progressive chest deformity and unimproved bone structure, the possibility of a remission is suggested by the prolonged course, the confinement of deformity to the vertebral column, and the clinical improvement in the hardness of bone and in general well-being. According to Tinz, spontaneous cure or arrest of the process has not been noted in male cases. Berger describes an apparent remission in a case after extreme deformity of chest and extremities had developed. In the case presented castration may have helped to exert a favorable influence.

The cause of osteomalacia is not known. The disease has been attributed to infection, errors of nutrition, and perverted glandular function. Organisms have been isolated from the blood of patients and of animals suffering with a similar condition. Organisms isolated from the blood of white rats have reproduced malacia after injection into other rats. Feeding experiments have suggested the relation of errors of nutrition. The theory of perverted glandular function has been most supported, and much work has been done in the attempt to fix the responsibility of the various ductless glands. The ovaries, hypophysis, adrenals, thyroid, and parathyroids have been thought to play a role, singly or as a part of a polyglandular syndrome.

The loss of calcium and the softening of bone, together with a new production of bone poor in lime are characteristic. There is a tendency to lime deposit elsewhere, as in the kidneys and bladder. McCrudden believes that osteomalacia is an exaggeration of a normal function, that the balance of bone metabolism is disturbed by excessive demands for calcium, as in pregnancies, bone tumors, and fractures. When bone katabolism exceeds anabolism the result is osteomalacia.

Treatment is empirical. Phosphorus, adrenalin, pituitrin, thyroid extract, arsenic, chloral, and chloroform narcosis have been among the remedies advocated. Since Fehling, in 1887, recommended castration in the treatment of osteomalacia in women, authors have reported as high as 80 per cent. of cures following operation. Sterilization by Roentgen rays has proved beneficial. Results were best in puerperal cases, which often tended to recover spontaneously; nulliparae were usually not benefited. Metabolic studies do not indicate that a mineral retention is produced after castration, as was supposed. Accordingly, many authors believe that the value of castration and sterilization lies only in the pre-

vention of future pregnancies. Although castration of male cases has been advised in the hope of producing results comparable with those reported in female cases, no report of the operation has been found in the literature.

Conclusions. Five years after castration the case reported shows no actual improvement in bone structure. A probable remission has occurred, which may have been influenced by the operation. The result of castration in this patient would seem to indicate that osteomalacia is not a disease of the sexual glands.

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AUTOINTOXICATION AND ITS TREATMENT BY (TRANS-) DUODENAL LAVAGE.

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Autointoxication is a toxic condition of the blood and lymph caused by substances generated through the influences of the vital processes of the organism.

Autointoxication occurs in two forms: (1) the histogenic, and (2) the enterogenic. The histogenic is due to abnormal function of the antitoxic glands and of the tissues; the enterogenic is caused by abnormal action of the digestive enzymes and of the bacteria upon the food. The result of this action is the generation of numerous poisons and noxious substances, which, unless neutralized or removed, are absorbed into and circulate in the blood and at length give rise to autointoxication.

As the vitiated blood reaches everywhere, any part of the body may become diseased through the influence of the circulating toxins, which manifests itself generally or in ways peculiar to the affected organ or tissue; for instance, as anemia, general malaise, migraine, facial neuralgia, nervousness, melancholia or other psychoses, goiter, circulatory disturbances, bronchial asthma, catarrh of the mucous membranes of the respiratory or digestive tracts or of the liver, attacks of vomiting or diarrhea, albumin or sugar in the urine, rheumatism, cutaneous outbreaks and in many other ways.

Clinically, the presence of excessive putrefaction, excessive fermentation, an acid reaction of the stool, or a combination of any of these is suggestive of some form of enterogenic autointoxication.

The diagnosis of the putrefaction of proteids is readily made by the indican test, but about the decomposition products of excessive carbohydrate fermentative and of faulty fat digestion so little is known, and they are so hard to trace except when abundant enough to cause acid stools, that this condition is rarely recognized, which naturally leaves much undone by way of treatment. The difficulty of dosing these toxins and the ease of making the indican test have caused the term autointoxication to become practically synonymous with putrefaction; but it is precisely the toxins from carbohydrate fermentation and faulty fat digestion, especially the volatile fatty acids, and of these more particularly lactic, acetic, and butyric acid, which constitute a potent cause of disease by lowering the alkalinity of the blood and lymph, acidosis so called.

The bacterial count, too, is uncertain and misleading as an index to autointoxication, for while the estimated normal of 125,000,000 bacteria in the daily stool is found much increased in simple fermentation with a corresponding increase in the proportion of the intestinal toxemia, their number may be greatly reduced if large amounts of chemical toxins, poisonous to them, are present (see Case VII).

As in chronic morphin poisoning, so in both histogenic and enterogenic autointoxication the gastro-intestinal tract is the principal channel of elimination for the toxins circulating in the blood.

Of the various methods of treatment the Metchnikoff and the elimination treatment are those most generally employed at the present time. The Metchnikoff treatment consists in making of

the intestinal contents a culture medium for the Bacillus bulgaricus, which, through the formation of lactic acid, creates an environment in which the putrefactive bacteria can no longer thrive. As a rule it quickly reduces the evidence of pure alkaline putrefaction, but is obviously contra-indicated whenever the volatile fatty acids or their derivatives are at fault. The elimination treatment consists in purgation and in colon irrigation; both give some relief, but purgatives are irritant and contra-indicated as a routine measure and colon irrigation cleanses at best only the large bowel.

Therefore, considering that it is unscientific to further increase the volatile fatty acids by the Bacillus bulgaricus treatment if they are already present in excess; that because of the difficulty and cost a thorough chemical stool examination though almost indispensible for proper treatment can rarely be made; that the circulating toxins are chiefly discharged into the intestine, and, finally, that purgation and colon irrigation are of limited usefulness, a wide application should await a method of treatment which because of its efficacy in all cases of autointoxication makes a complicated feces analysis in most cases unnecessary, and which combines all the good features but has none of the disadvantages of the Metchnikoff treatment, purgation, and colon irrigation. Such a method is (trans-)duodenal lavage, first described by the author.[1]

Duodenal lavage flushes out the entire length of the intestinal canal from pylorus to rectum; it bodily removes the toxins of whatever nature; it restores by simple cleanliness in the intestinal tract the conditions necessary for normal bacterial growth, as shown by the results obtained; in this way it lays the foundation upon which the curative forces of nature may build the structure of returning health.

For duodenal lavage to be effective the irrigating solution must be non-absorbable; it must be employed in bulk and be sufficient in volume to flush the bowels. Further, because of the taste, the intolerance of the stomach to the amount of solution employed and the necessity of overcoming the control of the pylorus, the solution must be introduced directly into the duodenum, which is accomplished by means of a duodenal tube.

The treatment is easy to take if skilfully given; it consumes only about fifteen minutes, and is followed within an hour by from one to three pleasant watery evacuations, the patient feeling light, free, and buoyant. No untoward effects have ever been observed.

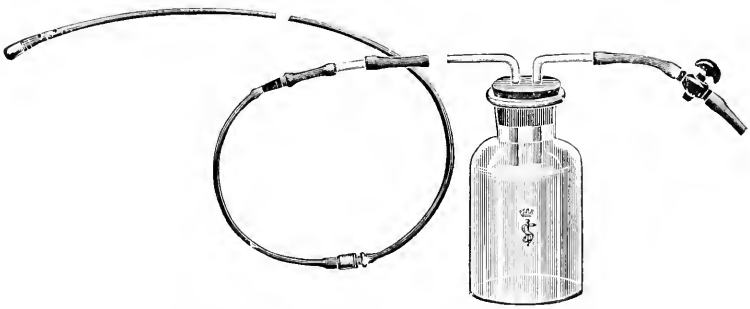
The writer uses a duodenal tube which can be manually introduced, and which, because of its small sinker, slips into and out of the duodenum easily, without the delay incidental to the ordinary

[1] Jutte, M. E.: Transduodenal Lavage; a New Method in the Treatment of Chronic Ailments, with Report of Results in Cases of Asthma and Pernicious Anemia, New York Med. Jour., March 16, 1912. Transduodenal Lavage: Treatment and Report of Some Cases of Chronic Diseases. Jour. Am. Med. Assn., February 22, 1913, lx, 586 and 587.

types of duodenal tubes. This invaluable fact permits the treatment to be carried out as a routine measure in the doctor's office.

A solution which usually passes through the bowel without being absorbed by the mucous membrane is one quart of water containing 9 grams each of sodium chloride and sodium sulphate. To make sure that the fluid will be passed on without being absorbed it is sometimes well to add a small quantity of saturated solution of phenolphthalein. Other medication may be added if indicated, such as sodium bicarbonate in acidosis, quinin in amebic dysentery, powdered medicinal soap (8 grains) in pancreatic insufficiency, resorcin in fermentation, chamomile tea for inflamed mucus surfaces. If silver solutions are indicated the sodium chloride should be replaced by an additional quantity of sodium sulphate.

The method of administration, improved in several details, is as follows: Prepare 1 quart of the solution at a temperature of 105° to 110° F. Moisten the tube and lubricate the interior by forcing a



Author's duodenal tube, with suction bottle.

dram of glycerin into it with a hypodermic syringe. Insert obturator to bottom of hollow stem of sinker. Protect patient's clothing with a rubber apron.

If the patient is nervous, spray the throat with a 1 per cent. cocain solution. The stomach must be empty. Then place the end of the tube on the back of the tongue; the patient should be told to swallow once, at which moment the tube is readily thrust over the root of the tongue. Then, during respiration and aided by occasional sips of water, gently finish the introduction of the tube to the 3-ring mark, step by step, with drawing the wire gradually. Permit the patient to lie down on a couch and turn well on his right side; connect the tube with a suction bottle, and after a minute or so exhaust the air from the bottle with a large size syringe.

The fluid returned becomes stringy the moment the sinker has passed the pylorus and struck enteric secretion, which occurs usually within one or two minutes. With a little practice this moment is easily ascertained, though the stringiness may be very slight.

Let the patient sit up; disconnect bottle and connect tube with container after discarding cooled-off fluid in leader. Let one and a half to two pints run in at a quick drip during from five to ten minutes. A momentary discomfort calls for a short pause. A tapered glass tip inserted in the connecting tube will regulate the rate of drip nicely. When finished let just enough plain warm water run through to rinse the tube. Withdraw tube gently during respiration.

To make the following case reports complete I must mention that in Cases VII to X, in which there was suspicion of excessive carbohydrate fermentation or faulty fat digestion, I withdrew carbohydrates and fats entirely and employed for a time the Salisbury diet, which consists chiefly in scraped or minced lean beef broiled, with plenty of warm water to drink between meals.

Of drugs, digestive mixtures, bile and pancreatic extracts, only were used.

The number and frequency of treatments depend on the severity of the case; in the average case I give the treatment every three or four days for one or two weeks, then weekly for one to three months, and after that at longer intervals.

The following cases, together with those of pernicious anemia, asthma, chronic bronchitis, jaundice, enteritis, etc., already reported, will give a fairly good idea of the wide field for the treatment:

CASE I.—Mrs. T., aged thirty years. A case of ptomain poisoning; had vomited numberless times during twenty-four hours. After a few hours of sedative treatment, patient managed to retain duodenal tube and take the lavage. Immediate and complete recovery after bowels had been flushed.

CASE II.—Mrs. D., aged twenyt-two years. Goiter, more prominent on right side; slight exophthalmos and severe cardiac and nervous symptoms. Received lavage about once a week for three months. Diet restricted to plain food. The goiter has come down in size gradually, and all the symptoms have uniformly improved.

CASE III.—Mrs. G., aged thirty-eight years. A case of chronic headache and general malaise. Had taken every kind of treatment without avail. For personal reasons treatment was crowded, so that within four weeks she received twenty-one lavages, ten thermopenetration treatments of the abdomen and ten injections of polyglandular extract. Improved steadily and markedly, with two slight attacks owing to indiscretion of diet.

CASE IV.—Mr. C., aged forty-six years; merchant. Had suffered for six weeks from diarrhea with loss of strength; extreme indicanuria. Had been confined to bed for several weeks. Duodenal lavage was given on eight consecutive days, then for two and a half months every second to fifth day, in all twenty-seven times. The indicanuria was unusually stubborn, the last trace disappearing not until

eighteen treatments had been given. After the first lavage a large round worm was expelled.

CASE V.—Mrs. S., aged fifty-eight years. A chronic case of "biliousness," accompanied by glossitis; skin was of a yellowish, unhealthy appearance. Received lavage once every five days to two weeks during three months; also vibration over the liver. The biliousness improved steadily from the beginning, the skin cleared up, and the glossitis had almost disappeared when seen last.

CASE VI.—Mrs. N., aged thirty-five years. Had suffered for six years from "biliousness," cholecystitis, general discomfort in hypogastrium, and had been for a long time on an ulcer diet; this was discontinued. Received eight lavages within two weeks. Marked progressive improvement in all her symptoms after the first treatment.

CASE VII.—Mrs. D., aged seventy-four years. Found patient suffering from paroxysmal tachycardia with a pulse of about 200, reflexly from gas pressure. Examination of urine and stool showed indican normal, excessive fermentation, enteritis, pancreatitis with inhibition of fat digestion, and autointoxication, due to carbohydrates and fats, with a coefficient of 800 to 100 (von Oefele), the bacteria being reduced to one-eighth of the normal. The acute condition was relieved by emptying the stomach and by a purgative. Another acute attack occurred three days later. A few days after that lavage treatment was commenced at the rate of once or twice a week, in all thirteen treatments. All fats and fermentative food were withdrawn. Much relieved from the beginning. After a few treatments the patient felt quite well, though at first there were occasional attacks of palpitation which finally disappeared. A subsequent stool examination showed a very great improvement in all respects.

CASE VIII.—Mrs. H., aged forty-two years. Had a very severe case of mucous colitis and had been under medical care for seven years; in bed for periods of months at a time on account of hemorrhages. Passed large amounts of jelly-like mucus. In May, 1915, received a daily lavage for five consecutive days; then one every second day for two and a half weeks; after that one every week or two. No drugs were given. From the beginning her condition improved rapidly, so that after a month she felt "fine;" no more hemorrhages have occurred. Takes treatment now merely to avoid recurrence.

CASE IX.—Mr. S., aged thirty-eight years; minister. Had suffered for eighteen years from bronchial asthma and general catarrhal condition of mucous membranes; also for fourteen years from a severe case of psoriasis, especially on face and chest. No previous treatment had availed anything, but camp life during the Spanish-American War had benefited him greatly for a time. Received lavage irregularly during eight weeks, in all about twelve times.

Improvement steady, so that he considered himself cured and finally discontinued visits. The psoriasis, too, paled away and disappeared, except for a few scales here and there.

CASE X.—Mr. B., aged sixty years; druggist. Complained for years of severe flatulence and almost constant tenesmus, with passages of small quantities of mucus and thin fermentative material; very nervous, wornout, dizzy; sallow complexion. Also nails coarsely ridged, extensively undermined and hanging on merely by the roots. Received lavage twelve times in one month; cut out all fermentative food. Improvement immediate, with eventual cure. The nails, too, showed an unexpected and rapid improvement, growing up on a rosy, healthy looking base.

COMPARATIVE STUDY OF THE TOXIC EFFECTS OF THE NATURAL AND SYNTHETIC SALICYLIC ACIDS.

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THE task which we originally proposed to ourselves in designing this series of experiments was that we should try to determine the toxic and fatal doses of the natural and synthetic acids and their salts. It was intended to present a brief view of this problem, molded by the inherent constitution of the two drugs. The clinical matter was dealt with only so far as it seemed to throw light on the relation of chemical structure to therapeutic or toxic effects; but it has been found necessary to make greater use of clinical observations, and to treat the whole subject in an evolutionary manner. We will begin with a brief statement of the theme.

Salicylic acid prepared from oil of wintergreen is slightly milder than salicylic acid prepared in other ways. This fact was noticed by Stokvis in 1896, but the discrepancy has remained unexplained, and, indeed, practically undiscussed by chemists and physiologists of late years.

In order to institute a comparison we have examined the acids and their sodium salts, which are to be easily procured, and we have made some clinical studies of the action of the following substances which may be described as complementary: Cinnamate of sodium, phthalic acid, saligenin, salicin, methyl salicylate. The principle recently elaborated by Zadek, who adopted it from Stricker, is one which we have followed. This principle is that salicylic acid is

the ultimate result of any reaction in the body in which these allied substances are concerned.

Comparisons between the two have been instituted by pharmacologists. Studies of this nature have been published by Waddell, Hewlett, Eggleston, and Hanzlik. Intelligent review of these papers is not easy; in much they may be sound, but a strong bias is manifest in all of them.

The dispute over the virtues of natural and synthetic salicylic acids has always been confined to America, and its consequences remain, so far as truth and science are concerned, in an undoubted exacerbation of medical jealousy and a rapid growth of prejudice and ignorance. European writers have not disputed over a subject which is, or ought to be, purely scientific. Probably they have not thought it worth while.

Stokvis gives a fair summary of the science. We have found it accurate, the only point of difference being that salicylic acid is today manufactured with more skill than it was in 1896. But whether the samples which are sold are still free from the injurious cresols and the therapeutically useless parahydroxy benzoic acid is a matter of doubt.

The specimens examined by Stokvis were analyzed by Van't Hoff, and were presumably pure. He tried three acids: one prepared from oil of gaultheria, one prepared from anthranilic acid, and one prepared from phenol. They were similar in all respects. As our results have agreed with those of Stokvis, we tested our samples in the same way.

Fischer states[1] that pure natural salicylic acid melts at 156.8° C., while commercial acid melts at 153.5° C.

According to Bloch,[2] even a small proportion of creosotic acid lowers the melting-point of natural and synthetic salicylic acids. We found:

Purity of the salicylic acids used as determined by titration with $\frac{N}{10}$ KOH: Natural, 98 per cent.; synthetic, 98.64 per cent. These acids were recrystallized three times from hot water and melting-points taken of each crystallization as follows:

	Natural.	Synthetic.
Original acid	156.2° to 157.8°	155.9° to 157.1°
First recrystallization . .	156.2° to 157.7°	156.2° to 157.5°
Second recrystallization . .	156.8° to 157.8°	156.8° to 158.0°
Third recrystallization . .	156.8° to 158.0°	156.8° to 158.0°

Salicylic acid does not melt sharply. The temperatures given here are the points where (1) the acid fuses sufficiently to flow, and (2) fusion is complete. According to Smith[3] the melting-point of the synthetic acid is 158.5.

[1] Pharm. Zentralbl., xlii, S. 327.
[2] Pharm. Jour., 1890, lxxii, 429.
[3] Ibid., 1915, p. 617.

The original acids were sublimed, sublimates being taken at intervals. The recrystallized acids (third recrystallation) were also sublimed. Their melting-points were as follows:

	Natural.	Synthetic.
First sublimate	155.8° to 157.0°	156.0° to 156.8°
Second sublimate	156.0° to 156.8°	156.0° to 156.8°
Recrystallized	156.0° to 156.9°	156.0° to 156.7°

The lower melting-points of the sublimed acids are no doubt due to a slight decomposition into phenol, the presence of which tends to lower the melting-point.

Solutions of sodium salicylate (25 per cent.) were prepared by dissolving the acids, together with sodium bicarbonate, in molecular proportions as follows:

Salicylic acid, natural (98 per cent.)		22.0050
Sodium bicarbonate (99.7 per cent.)		13.1624
Water	q. s. to make	100.0 c.c.
Salicylic acid, synthetic (98.64 per cent.)		21.8622
Sodium bicarbonate (99.7 per cent.)		13.1624
Water	q. s. to make	100.0 c.c.
Sodium salicylate, natural (25 per cent.).		
Sodium salicylate, synthetic (25 per cent.).		
Specific gravity at 20° C.	1.10276	1.10275
Optical rotation	0°	0°

It may, therefore, be concluded that we are dealing with the same chemical structures. The following is a summary of Stokvis's papers:

Charteris and Maclennan showed a considerable difference between the acid prepared from oil of gaultheria and the synthetic acid. The results led both authors to the conclusion that the artificial acid, in spite of chemical purity, for no cresols were found, must be ranked as a physiologically impure substance. In comparing salicylic acids made from phenol with that prepared in other ways, we, of course, included the natural acid. As the interest of the subject is chiefly theoretical, we instituted our comparison by the experimental method. The phenol salicylic acids used, the anthranilic acid, and the acid prepared from oil of gaultheria are chemically the same. Solubility, elementary analysis, and polarization as tested in the laboratory of Van't Hoff, gave the same results. The molecular arrangement of three acids was identical, which would imply physiological identity. But in the animal experiment the case was different.

Sodium salicylate was used in all experiments. They fell into three parts: excretion and changes in the urine, the toxic and lethal doses, the physiological action in men.

The acid prepared from oil of gaultheria manifested a more rapid rate of excretion.

The cause of this quicker excretion is twofold: The natural acid is less active than the others. In rabbits, clear signs of poisoning appeared after large doses, 700 to 800 mg., the fatal dose being 1300 to 1400 mg. per kilogram of the animal's weight. Toxic effects were manifested by profound disturbance of the central nervous system and respiration, paralysis of the hind legs, dyspnea, stupor. Of great interest is the fact that the acid prepared from oil of gaultheria produced almost no tremor, which, however, in the case of the other acids, appeared constantly after doses of 700 to 900 mg., together with convulsions. These toxic symptoms were entirely wanting to the action of the gaultheria acid. Given the same animal and the same doses there was less disorder after the natural acid. The fatal dose, however, of the three acids was nearly the same.

As an extension of these researches, Dr. Morel undertook some on himself. The effects on pulse, temperature, appetite, and other functions were less marked in the case of the acid prepared from gaultheria. The rate of breathing was constantly raised by the phenol and anthranilic acids, but the natural acid caused virtually no change in the respiration.

It appears from these researches that the quantitative difference between the acids is so clearly demonstrated that we must agree wholly with the conclusion of Charteris and Maclennan when they pronounce the natural acid less toxic. To explain this difference, one must consider the greater ratio of excretion of the natural acid, which is due to the greater osmotic properties.

This is not only a sufficiently complete account, for practical purposes, of the systematic side of the subject, but is full of precisely that relation of the living organism to the chemical structure of the drug employed which can be treated properly only by a writer who knows chemistry and physiology, but has a great practical knowledge of the difference between the animals themselves. Rabbits and guinea-pigs are less sensitive than dogs, and dogs less sensitive than men, while human beings in health and disease show marked variations of physiological response to the salicylates.

In the following experiments we began with the intravenous method of injection, next we undertook subcutaneous injection, and lastly administration by the stomach tube. Clinical observations extending over many years are introduced, but in the form of a summary, as it would be impossible to report them in detail. They are introduced merely for the purpose of throwing light on the toxic and fatal doses of the various salicylates.

Injections of sodium salicylate under the skin are very painful, while it is most difficult to inject solutions of the salicylic acids into the veins. It was found that alcoholic solutions caused necrosis at

the point of the injection into the ear vein of rabbits. In intravenous injection the formula cited by Hasenfeld is the best:

Sodium salicylate	8.0
Caffeine sod. salicylate	2.0
Water or saline	50.0

Dissolve and filter.

The injections were begun in April, 1915, and continued to June, 1916, in four series of animals. In human cases, injections were begun several years ago, men being already reported.

INTRAVENOUS INJECTIONS. Second series: In testing the effects and comparative lethal doses of synthetic and natural sodium salicylate, 8 rabbits, averaging $3\frac{1}{2}$ pounds each, were used—4 for the synthetic and 4 for the natural salts.

Intravenous injections were given, using the marginal ear veins, beginning with 200 mg. and increasing 100 mg. at a time until 800 mg. was reached.

Practically no symptoms developed from either the synthetic or natural salts, and it was impossible to see any difference between the two salts. Rabbits injected with 800 mg. of either the synthetic or natural salts died almost immediately after receiving the injection.

These injections were given twenty-four hours apart to permit the rabbits to eliminate the salts and to recover from the shock of the previous injections.

The only obvious symptoms of these injections short of the lethal dose was a rapid necrosis of the ears of the rabbits injected.

CONCLUSION. There is, in rabbits, no very obvious difference in the toxic action between synthetic and natural sodium salicylate when injected intravenously.

SUBCUTANEOUS INJECTIONS. Subcutaneous injections of synthetic and natural sodium salicylate failed to show any difference in toxicity. As these injections were very painful to the rabbits they were not carried beyond 800 mg., which was not lethal, and in fact produced no symptoms excepting those of extreme pain at the sight of injections, which subsided in from five to ten minutes.

Administered through Stomach Tube. The rabbits averaging $3\frac{1}{2}$ pounds in weight were given respectively 1.5 gms. of natural and synthetic sodium salicylate dissolved in distilled water, administered through stomach tube, the stomachs of both animals being empty. The only symptoms of the above amounts were that rabbits were very quiet for an hour and a half, after which period they ate carrots with normal relish. At frequent intervals the animals were made to move about their cages, but no signs of paralysis were observed.

This treatment was continued at twenty-four-hour intervals, increasing each dose by 1.5 gm. (without any symptoms with the exception that the rabbits waited, before eating, for longer and

longer periods of time after treatment). Following the introduction of 6 gms. of the natural and synthetic salts, both rabbits showed symptoms of distress, and shortly became paralyzed. The rabbit that had been given the synthetic salt showed constantly increasing severity of symptoms, and finally became completely paralyzed, and died seven hours after receiving 6 gms. of the synthetic salt.

The rabbit that received the 6 gms. of the natural salt showed immediate symptoms of distress and became partially paralyzed, but those symptoms gradually subsided, and the following morning the animal ate carrots and bread without difficulty, and with seeming relish. This rabbit lived about two weeks and seemed to be normal in every way, but it died suddenly just after eating carrots. Autopsy failed to show any stomach lesions, but the liver showed extensive coccidiosis infection.

The synthetic rabbit, on autopsy, showed an inflamed stomach distended with fecal matter; other organs seemed to be macroscopically normal.

Second Pair of Rabbits Given Salts by Stomach. The above test was repeated with two rabbits weighing 4 pounds each. One rabbit received 5 gms. of natural sodium salicylate and the other one received 5 gms. of synthetic sodium salicylate, dissolved in 10 c.c. of distilled water and made up to 40 c.c. when administered by stomach tube. Both showed slight signs of distress in a few moments, but soon settled down quietly in their cages, neither showing any inclination to eat or drink. The natural rabbit died in three and a half hours without having developed any marked symptoms or signs of paralysis.

The rabbit that received the synthetic salt died some time during the night, but at the time of the death of the rabbit that received the natural salt the rabbit that had received the synthetic salt, while he would not eat, seemed in very good condition.

Postmortems of both of the above animals showed badly inflamed stomachs that were very much distended and filled with fecal matter.

Third Pair of Rabbits Given Salts by Stomach. These rabbits weighed $3\frac{1}{4}$ and 4 pounds. The $3\frac{1}{4}$-pound rabbit was given 4 gms. of the natural salt and the 4-pound rabbit was given 4 gms. of the synthetic salt. Both animals, like previous ones, became very quiet in a few moments and refused to move about their cages unless forced to, neither, however, showing any signs of paralysis.

In three hours and a half after ingesting the salt the natural rabbit was suddenly seized with a convulsion and died in a few moments. Postmortem showed a badly inflamed stomach distended with fecal matter.

The synthetic rabbit, however, drank freely of water and ate a carrot about four hours after ingesting the salt, and is still alive and eats well, but shows marked disinclination to move about.

CHART I.

	Doses given intravenously.	Date.	Temperature at time of injection.	Time of injection.	Temperature readings at five-minute intervals after injection.									
					5 min.	10 min.	15 min.	20 min.	25 min.	30 min.	35 min.	40 min.	45 min.	50 min.
		1915												
Natural salt	200 mg.	June 17	37.0° C.	2.40 P.M.	37.4° C.	38.0° C.	38.0° C.	36.0° C.	35.0° C.	36.0° C.	37.0° C.	37° C.	37° C.	
Synthetic salt	200 mg.	June 19	37.0° C.	10.45 A.M.	38.0° C.	38.0° C.	38.0° C.	37.5° C.	37.0° C.	37.0° C.	36.8° C.	37° C.	37° C.	37° C.
Synthetic salt	200 mg.	June 22	36.8° C.	5.45 P.M.	36.6° C.	37.4° C.	38.0° C.	37.4° C.	37.0° C.	37.0° C.	37.0° C.	37° C.	37° C.	37° C.
Natural salt	200 mg.	June 24	37.2° C.	11.40 A.M.	38.2° C.	38.0° C.	37.8° C.	37.8° C.	37.5° C.	37.2° C.	37.0° C.	37° C.	37° C.	37° C.

Weight of rabbits, $2\frac{3}{4}$ pounds; same rabbit for both tests.

CHART II.

	Doses given intravenously.	Date.	Temperature at time of injection.	Time of injection.	Temperature readings at five-minute intervals after injection.									
					5 min.	10 min.	15 min.	20 min.	25 min.	30 min.	35 min.	40 min.	45 min.	50 min.
		1916												
Natural salt	200 mg.	June 17	37° C.	2.40 P.M.	37.4° C.	38° C.	38° C.	36.0° C.	35° C.	36° C.	37.0° C.	37° C.	37° C.	
Synthetic salt	200 mg.	June 19	37° C.	10.45	38.0° C.	38° C.	38° C.	37.5° C.	37° C.	37° C.	36.8° C.	37° C.	37° C.	37° C.

Conclusion. There is apparently no difference in the toxic and and irritant properties of synthetic and natural sodium salicylate in large doses. What the effects of the therapeutic doses administered to rabbits over a considerable period of time are is a question that can only be answered by a series of long and careful experiments, which we are now undertaking.

In experimenting with large doses the individual equation of the animal seems to count for more than the weight of the animal or the amount of the drug administered.

Temperature Experiments. Here, again, rabbits differ from dogs in their behavior to the salicylates. Whereas dogs showed no drop in temperature, the curve in rabbits was irregular, from which it is difficult to deduce a rule.

SUBSEQUENT EXPERIMENTS—SUMMARY.

Natural Sodium Salicylate.

Rabbit.	Date.	Injected, mg.	Symptoms.	Weight of rabbit approximately three pounds.
No. 1.	Oct. 9, 1915	200	4.30 P.M.	No symptoms.
	Oct. 14, 1915	300	3.25 P.M.	" "
	Oct. 15, 1915	400	4.25 P.M.	" "
	Oct. 15, 1915	500	11.10 A.M.	" "
	Oct. 15, 1915	600	4.30 P.M.	" "
	Oct. 16, 1915	700	11.20 A.M.	Slight symptoms of shock, with rapid recovery.
No. 2.	Oct. 15, 1915	600	2.30 P.M.	No symptoms.
2.	Oct. 15, 1915	700	4.00 P.M.	Slight symptoms of shock with rapid recovery.
3.	Oct. 18, 1915	800	4.55 P.M.	Died immediately after injection.
4.	Oct. 18, 1915	800	5.10 P.M.	Died immediately after injection.
5.	Oct. 18, 1915	400	5.20 P.M.	No symptoms.
5.	Oct. 20, 1915	600	10.40 A.M.	Incoördination for a few minutes; rapid recovery.

Synthetic Sodium Salicylate.

No. 1.	Oct. 9, 1915	200	4.20 P.M.	No symptoms.
1.	Oct. 14, 1915	300	3.20 P.M.	" "
1.	Oct. 14, 1915	400	4.30 P.M.	" "
1.	Oct. 15, 1915	500	11.15 A.M.	" "
No. 2.	Oct. 15, 1915	400	2.35 P.M.	No symptoms.
2.	Oct. 15, 1915	500	3.30 P.M.	" "
2.	Oct. 16, 1915	600	4.20 P.M.	" "
2.	Oct. 17, 1915	700	11.15 A.M.	" "
No. 3.	Oct. 16, 1915	800	2.45 P.M.	Died immediately after injection.
No. 4.	Oct. 16, 1915	800	3.00 P.M.	Died immediately after injection.

Experiments in Dogs.—Vinci has reported the results of experiments in dogs. He administered sodium salicylate subcutaneously in a few instances intravenously and by the stomach tube. He

noted collapse, with fairly quick recovery, attempts to vomit, and salivation. He used the synthetic acid of Bayer.

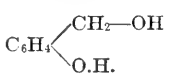
Collapse and salivation were the chief symptoms in our experiments with doses of 4 gms. in a dog weighing 8 kgs. The animal recovered. During convalescence there was weakness, also a dragging of the hind legs. The temperature did not fall.

Experiment, Fourth Series. September, 1915. Black, short-haired mongrel, 8 kgs.; 11 A.M., subcutaneous injection of 4 gms. natural sodium salicylate in 20 c.c. saline solution. Injection very painful. Salivation: dragging of legs. Recovery. The motions of the dog were at first excited, then stupid, then like collapse.

Toxic Doses. There is virtually no difference between the natural and synthetic acids except a difference arising from the less irritant action of the former. It is better borne by the stomach, and this fact slightly affects the toxicity in human beings. In rabbits the fatal dose was found to be 900 mg. to the kilogram of body weight. Toxic effects in dogs were noted after 0.5 gm. to the kilogram. Fatal doses were not tried. According to Vinci the fatal dose in dogs is 0.2 to 0.5 gm. to the kilogram of body weight.

Fatal Cases. We have been unable to find the report of any case fatal after the natural acid. Most of the deaths recorded were caused by sodium salicylate, and presumably the commercial product.

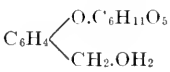
Comparative Clinical Effects. To make sure of obtaining a natural product through chemical changes in the living organism it is well to prescribe salicin. This glucoside is hydrolyzed in the organism, with the ultimate formation of salicylic acid, *e. g.*:



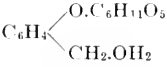
Salicin compares favorably with the synthetic salicylates. It has less action on the stomach and digestion. It was administered in 30 cases at the University and Bellevue Hospital Medical College and the Vanderbilt Clinic. The 5-grain tablets in use at these clinics are too small a dose. Twenty grains every four hours is the most satisfactory, but in these doses, as Dixnenf has pointed out, salicin must be carefully employed.

Acute Rheumatism. Saligenin, or salicyl alcohol, was used in 6 cases. Thirty grains were given three times a day. It is more powerful than salicin, is more effective, and in these doses produced noises in the ears and some salivation. It must be used with care.

The reason for the powerful effects of saligenin may be that it has a phenol and an alcohol group arranged thus:



Salicin, which is less active, is a monoglucoside, a natural product of saligenin, in which glucose is substituted for the phenol nucleus, *e. g.:*



Phthalic Acid. It is stated by Juvalta that phthalic acid is oxidized into salicylic acid and phenol. Mosso, however, was unable to confirm this result. He apparently leaves it undetermined after experiments which he says are insufficient. Stockman has recently spoken of phthalic acid as mediocre in its effects.

Phthalic acid as cotarnine phthalate was used in 3 cases of acute rheumatism. Its action on pain is very satisfactory. Phthalic acid is decomposed completely in the human organism:

Sodium cinnamate was used in 60 cases by subcutaneous injection. The injections are very painful unless controlled by anodynes. It is effective if it can be given in large enough doses, but owing to its relatively slight solubility it is not easy to employ more than 1 gm. at a time.

Methyl salicylate, used locally, has an excellent, if passing, effect on the pain and swelling of acute rheumatism.

Factors in Cases of Poisoning. It was clearly shown by Mlle. Chopin, in her thesis, that sodium salicylate is more quickly excreted in children than in adults and more quickly in healthy adults than in nephritics. The inference is fairly obvious. Salicylic acid or sodium salicylate tends to be more toxic when the kidney is impaired. Other causes affecting toxicity, as we have noticed, are: (1) Alcoholism; in these cases the salicylates should be given with caution. (2) The state of the stomach. (3) Diseases of the alimentary tract affecting the oxidizing of the benzol nucleus all increase the toxic effect of the salicylates. (4) Salivary glands. Salivation is always the symptom that precedes collapse, though delirium may occur first. Flushing of the skin is an early symptom of poisoning, especially worth notice, if nose-bleed occurs, too. Deafness and noises in the ears are very early symptoms. Disorders of the sense color, in which things look greenish or greenish yellow, as patients describe their perceptions, are late signs often noted during convalescence. The musical sounds, wholly abnormal and very disquieting, are intermediate between the period of rising cerebral disorder and dangerous collapse.

An experience of several years shows that these symptoms are almost equally incidental to both acids when pure, though they occur less frequently after the acid prepared from oil of birch or

gaultheria. In this respect the opinions of Latham and of Stokvis hold good today.

Fatal cases are recorded by different authorities. Vinci describes one after 35 gms. of sodium salicylate, the largest dose ever taken at a time. Headache, delirium, salivation, and coma, ending in death, marked the course of poisoning, as they do in others. In nearly all instances a cumulative effect, first noticed by Dixneuf, is reported. Such cases are not infrequent; instances are described by Sée, Chopin, Georges Huber, Wattelet, Quincke, Petersen, Empis, Heffermann, Binz, Koelin, Leonhardi-Aster, Fürbringer, von Jaksch, Wittich, Bertagnini, and Buss.

Conclusions. 1. When pure samples, whether natural or synthetic, are used the effects in animals are virtually the same.

2. The difference between the natural and synthetic salicylates in men is somewhat more distinct. In the case of the natural acid when administered to adults there was less gastric disturbance, the cerebral effects were slighter, and in general it may be said that this substance is better borne than the commercial acid.

3. It is not so toxic in very large doses, though when more than 75 grains are given in twenty-four hours there is a tendency to delirium in the susceptible to salivation and flushing of the integument.

4. The noises in the ears are noticed on the second day, as a rule, of administration.

5. It seems clear that the natural acid has less cumulative effect.

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REVIEWS

A Manual of Physical Diagnosis. By Austin Flint, M.D., LL.D., Late Professor of the Principles and Practice of Medicine and of Clinical Medicine in Bellevue Hospital Medical College. Seventh edition, revised by Henry C. Thacher, M.S., M.D., Associate in Medicine in the College of Physicians and Surgeons of Columbia University; Assistant Attending Physician, Roosevelt and Lincoln Hospitals, New York. Pp. 381; 20 illustrations. Philadelphia and New York: Lea & Febiger, 1917.

After an interval of five years the seventh edition of Austin Flint's well-known *Manual of Auscultation and Percussion* appears under the auspices of a new reviser. The first four editions, appearing between the years 1876 and 1885, were revised by the author; the fifth, revised by J. C. Wilson, appeared in 1890; the sixth by Haven Emerson in 1912. A comparison with the six previous editions reveals a steady but small growth both of the book and of the subject, which stands, however, in marked contrast to the enormous development of most medical subjects during the same period.

In a work of such historical interest it seems unfortunate that the title of the present edition had to be changed to that of a *Manual of Physical Diagnosis*, even though it was necessary to include pulse-tracings and other subjects that could not properly be included under the head of auscultation and percussion. The omission of an important chapter on the physical examination of the nervous system, which had been introduced into the fifth edition, is also to be regretted. The space thus gained has been devoted to an opening chapter on the physics of sound. The other two extra chapters of the fifth edition (on the abdomen and on the order of physical examination) have been retained.

The general form of the early editions, which so clearly and accurately present the essentials of a large subject in a small space, has been adequately maintained. E. B. K.

The Early Diagnosis of Tubercle. By Clive Riviere.

The subject with which this small hand-book deals is of the greatest importance to every practitioner of medicine, as upon it depends not only the cure of the patient but also the prevention

of a possible source of infection to other individuals. The book presents the subject in a very accessible form, which renders it convenient for reference, the reading matter being concise and to the point. This is especially true of that portion of the book dealing with the physical examination of the patient, in which the various steps are well arranged and contain many points in the examination which, although they may appear trivial, are of the utmost importance in the carrying out of a careful examination in a doubtful case. It is to be regretted that the effort to be brief and concise has led the author to abbreviate this most important section of the book.

Undue prominence is given the sections on tuberculin and the use of the roentgen-rays, which are usually not available in the average patient. The chapters on sputum and temperature, while very good, would be improved if allotted some of the space devoted to the special tests above mentioned. The section on tuberculosis in childhood is mainly of value in calling attention to this condition and leading to a more thorough study of the chests of children in which tuberculosis is suspected. The value of the physical signs in the illustrative cases would be considerably increased if they were supported by autopsy findings instead of skiagrams.

Anyone interested in the careful examination of the chest will find in this small volume a great deal of valuable information, arranged in such a manner as to be readily accessible, very readable, and concise. F. A. C.

Pharmacology and Therapeutics: For Students and Practitioners of Medicine. By Horatio C. Wood, Jr., M.D., Professor of Pharmacology and Therapeutics in the University of Pennsylvania; Second Vice-Chairman of the Committee of Revision of the U. S. Pharmacopœia. Second edition. Pp. 455; 28 illustrations. Philadelphia and London: J. B. Lippincott Company.

The value of Dr. Wood's original edition of this work and numerous recent advances in pharmacology and therapeutics have demanded this revision. Its publication has been delayed sufficiently to bring it into complete conformity with the new *United States Pharmacopœia*. All the official drugs are included, although the author explains that some of them are of little value, and some unofficial drugs are recognized because of their practical importance. The substitution of "mil" for C.c. is made, but the metric doses are still parenthesized.

The first chapter includes definitions, weights and measures, prescription-writing, incompatibilities, etc., while the rest of the book is devoted to the drugs. These are arranged in groups accord-

ing to their effects: for instance, those affecting secretion are taken up together, likewise those affecting the nervous system, the circulatory system, etc. In each instance they are first discussed briefly as a group, and then each drug is considered in regard to its materia medica, physiological action, and therapeutic uses. At the close of the discussion of the drugs in each group are given references to the literature, this feature adding greatly to the value of the text-book.

On the whole this book seems to the reviewer concise and yet sufficiently elaborate for students and practitioners, somewhat dogmatic and yet eminently practical in its presentation of only the important facts in relation to drugs. T. G. M.

THE ANIMAL PARASITES OF MAN. By H. B. FANTHAM, M.A., Lecturer on Parasitology, Liverpool School of Tropical Medicine; J. W. W. STEPHENS, Jones Professor of Tropical Medicine, Liverpool University, and F. V. THEOBALD, M.A., Professor of Agricultural Zoölogy, London University. Partially adapted from Braun's *Die Tierschen Parasiten des Menschen* (4 ed., 1908), with an appendix by Dr. OTTO SEIFFERT. Pp. 900; 423 illustrations. New York: William Wood & Co.

THE present volume is a translation and elaboration of Braun's standard work on parasites, but with such a vast amount of new matter and so many alterations that the identity of the German work has largely disappeared. The introduction remains much the same, with modifications according to the English authors. The new edition contains many references to general parasitism. Fantham has undertaken the classification of the protozoa, and has followed very closely after the original. He, however, uses the class name of Sarcodina of Bütschli in place of Rhizopoda, and traces the history of development of these organisms to some extent. The section of Flagellata, especially the Trypanosomes, has received very great elaboration, and the Leishmania are well described. Under Coccidiidea the authors have used the genus name of Eimeria of Schneider for Coccidia of Leuckart. The section on Hemasporidia has received considerable amplification, much attention being given to Theileria and Babesia. Chlamydozoa are treated generally at the end of the section on Protozoa, but one misses the Kurloff bodies, a structure upon which many original observations have been made. Platyhelminths have been treated by Dr. Stephens, who has lengthened the general description and adopted an almost entirely new classification largely based upon older writers, but also upon some work appearing since the German edition. His

treatment of the Nemathelminths has followed the same character. A few of the genus names have been changed.

Following this capital comes a short chapter on the observation, preservation, and cultivation of Platyhelminths and the Nematodes. This is followed as before by Acanthocephala and Hirudinea. Theobald has written the section on Arthropoda, and greatly enlarged it by including newer additions and putting in keys to the various families and genera. The flies and mosquitoes have received much attention. The next section, called addenda, cites some of the rarer parasitic manifestations, *e. g.*, myiasis, and means to combat them.

A supplement of over one hundred pages reviews concisely the pathogenic relations of the animal parasites, and gives specific treatment. The remainder of the book is given over to appendices on Protozoölogy, including recent researches, culture media and technic, and on Trematodes and Nematodes, in which a few unusual findings and results are discussed.

At the end of the text all the references are collected according to subjects, with a guide to the page or pages on which each is discussed, and the names are arranged alphabetically. In former editions these lists were given after each subject, in many ways a preferable arrangement. The index is very full and satisfactory. Many illustrations have been added and the old ones much improved in reproduction. The book is a splendid systematic reference work and as well a text-book of pathogenic parasitology.

H. F.

A Text-book on the Practice of Gynecology. For Practitioners and Students. By W. Easterly Ashton, M.D., LL.D., Professor of Gynecology in the Graduate School of Medicine of the University of Pennsylvania. Sixth edition, thoroughly revised. Pp. 1097; 1052 drawings. Philadelphia and London: W. B. Saunders Company.

The sixth edition of this book upholds the prestige that has been gained by the former editions, and contains much additional matter. Several of the chapters have been extensively revised, with a resulting improvement in the book as a whole. The great value of this work lies in the fact that the author takes nothing for granted on the part of the reader's knowledge, and minutely describes the smallest details, to the end that even the novice must understand the technic and rationale of the various gynecological measures advised. Viewed from a critical stand-point, however, the failure to even mention radium is a noticeable omission in a chapter on cancer of the uterus that is otherwise excellent, and a brief description of adenomyoma would not be out of place. Likewise, the

usefulness of pyelography might be mentioned in considering diseases of the kidneys. The book is rapidly assuming huge proportions, giving evidence of the advances which have been constantly made in this field, and unless some of the subject matter is curtailed it is probable that future editions may be in two volumes.

To the student and general practitioner this work will undoubtedly continue to be a valuable aid, but, on the other hand, there is nothing unusual about the book that is of particular interest to the specialist. F. E. K.

CARE OF PATIENTS UNDERGOING GYNECOLOGICAL AND ABDOMINAL PROCEDURES BEFORE, DURING AND AFTER OPERATION. By E. E. MONTGOMERY, A.M., M.D., LL.D., F.A.C.S., Professor of Gynecology in Jefferson Medical College; Gynecologist to Jefferson and St. Joseph's Hospitals; Consulting Surgeon to the Philadelphia Lying-in Hospital, the Jewish Hospital, the Kensington Hospital for Women, and the American Oncologic Hospital. Pp. 144; 61 illustrations. Philadelphia and London: W. B. Saunders Company.

THIS interesting monograph, detailing the practice of the author, supplements the usual teaching of pelvic surgery to the medical student or nurse. To the often perplexed intern or nurse fresh on a surgical service it answers the question of how to do this or that minor procedure necessary to the comfort and well-being of the patient. The operating-room assistant or nurse may profit from a study of the illustrations if nothing else. The teaching is safe, well founded, and eminently practical. P. F. W.

DISEASES OF INFANCY AND CHILDHOOD. By L. EMMETT HOLT, M.D., Sc.D., LL.D., Professor of Diseases of Children in the College of Physicians and Surgeons (Columbia University), New York, and JOHN HOWLAND, A.M., M.D., Professor of Pediatrics in the Johns Hopkins University, Baltimore. Seventh edition. Pp. 1180; 215 illustrations. New York and London: D. Appleton & Co.

IN the seventh edition of this standard work the excellence of the former editions is continued and the book is made more valuable by complete revision in many places, bringing all the chapters up to date.

In Part I are found the instructive chapters on hygiene, and care, growth and development and peculiarities of disease in

children. In the latter chapter, as might be expected, stress is laid upon the physical examination of babies and children. The section on nutrition has been considerably enlarged and changed, and embodies all the newer ideas of value in this rather extensive and rapidly advancing field. Especially full chapters are included on hereditary syphilis and influenza, and a separate chapter deals with epidemic catarrh or la grippe. The pathology of the diseases of the heart and kidneys, and especially of the intestine, is fully discussed and well illustrated.

The reviewer has been accustomed to consider Dr. Holt's book in the light of the "Bible of Pediatrics," and believes it to be as complete and thorough as a single volume text-book can be made. Indeed, it would seem that it should be in the library of every physician whose practice brings him into contact with children.

A. G. M.

Losses of Life in Modern Wars: Austria-Hungary and France. By Gaston Bodart, LL.D. Military Selection and Race Deterioration. By Vernon Lyman Kellogg, Standford University. Edited by Harald Westergaard, LL.D., Member of the Committee of Research of the Division of Economics and History of the Carnegie Endowment for International Peace. Pp. 207. Oxford: At the Clarendon Press, Humphrey Milford.

One's favor is immediately elicited for this book, as well as for its companion upon *Epidemics Resulting from Wars*, on account of the handsome way in which it is constructed. The binding is blue cloth, the pages of the best paper, the type large and distinct, and the tables, of which there are many, in full-size type and never crowded. These features are especially noteworthy in view of the present tendency of some publishers to make use of cheap materials and to put the most possible on the individual page.

The first division of the work consists of two parts: the first dealing with the wars of Austria-Hungary between 1618 and 1913, and the second with those of France between 1614 and 1913. The available data upon the human losses of these wars are presented elaborately in tables, and the text on the basis of the tabulated figures makes out a case against war. Exception may be taken, however, to the conclusion drawn at the close of this division of the book that the present stagnant condition of France may be looked upon as a result of her preëminence as a war-like nation. The former premise is to be questioned in view of the part France is now playing in the European war.

In the final part of the work Kellogg presents a preliminary report and discussion upon the race-deteriorating influences of war. He makes three points: (1) that the men who are most fit mentally

and physically are the ones lost in war, the less fit being left for the reproduction of the race; (2) that the influence of the Napoleonic wars was to reduce the stature of the French male population and to increase their youthful infirmities and disease; (3) that venereal diseases are increased during war and that their effects are racially deteriorating. The facts submitted in substantiation of these conclusions are convincing and will be difficult to refute.

T. G. M.

The Obstetrical Quiz for Nurses. A Monograph on Obstetrics for the Graduate and Under-graduate Nurse in the Lying-in Room. By Hilda Elizabeth Carlson. Pp. 305. New York: Rebman Company.

The familiar plan of a quiz compend serves as a form for this excellent treatise on obstetrics for nurses. While the text is therefore necessarily shortened at times, the essential principles are presented with sufficient thoroughness to afford a clear description of the subject at hand. From the form of the book it should be of value in teaching obstetrics to nurses. The book is divided into twenty chapters which take up the various subjects of obstetrics. There are chapters on modifications of cows' milk, preparation of solutions and enemata and a brief description of the various measures used to alleviate the pains of labor. A careful study of the book will place a nurse in a state of preparedness to efficiently assist the physician and properly care for her patients. An essential feature is a description for improvising many things needed on an emergency or complicated case, outside of the maternity. The book is highly commended to nurses and teachers of nurses.

P. F. W.

Manual of Surgical Anatomy. By Lewis Beesly, F.R.C.S., Lecturer on Surgery and Operative Surgery, Edinburgh School of Medicine, and Lecturer on Surgical Applied Anatomy, Edinburgh Postgraduate Courses, and T. B. Johnston, Lecturer and Demonstrator of Anatomy, Edinburgh University, and Lecturer on Medical Applied Anatomy, Edinburgh Postgraduate Courses. Pp. 537; 164 illustrations. New York: William Wood & Co.

The writer of a book on surgical anatomy attempts a difficult task in deciding how much attention he should give to the surgical and how much to the anatomical side of the subject, for the book that covers the whole range on both sides has not yet been written. The authors have presented an excellent combination of the two.

The particular purpose has been to encourage the study of surgical anatomy from dissections, which all recognize is the best way to study gross anatomy for any purpose. Only the undergraduate student, however, can avail himself of this method of study, as a rule. The anatomy of surgical operations has been emphasized, without including the details of surgical technic. Special attention is given to the relations which the ends of the diaphyses and the epiphyses bear to the capsules and synovial membranes of the adjacent joints. A fund of valuable information concerning the anatomical aspects of a large number of surgical conditions is compressed within the 537 small pages. The illustrations, especially the colored ones, are very good, and are well selected to show the value of a special knowledge of the anatomy of certain regions. Those showing sections of the joints are particularly instructive. A feature is also made of roentgen-ray illustrations. The whole book serves well the very useful purpose of proving the value of a practical knowledge of anatomy. T. T. T.

Disorders of the Sexual Function in the Male and Female. By Max Hühner, M.D., Chief of Clinic, Genito-urinary Department, Mount Sinai Hospital Dispensary, New York City. Pp. 318; 4 illustrations. Philadelphia: F. A. Davis Company.

In realization of the dearth of information by genito-urinary specialists on the sexual neuroses as manifested by their text-books and personal admissions, the author has produced this short and practical treatise on the subject. Hühner, by virtue of his experience and technic in the treatment of the lower urological affections is far better qualified to present such a subject than the neurologist, upon whom in the past this responsibility has largely rested.

The author has refrained from entering upon the purely neurological aspects of the sexual disorders, except as a matter of elucidation; nor does he discuss psychanalysis or the various types of sexual perversions. These he refers to the neurologist as their pathology belongs to the domain of abnormal psychology. The author also chooses to disregard the venereal diseases in their connection with the subject under discussion. Sterility, likewise, is omitted since it has been accorded an independent treatise.

Thus the subject matter of the book comprises chapters devoted to masturbation, impotence, pollutions, priapism, satyriasis, nymphomania, dyspareunia, absence of orgasm in the female, enuresis, withdrawal, continence, etc.

The conciseness and practical manner of presentation recommends the work as an introduction to the subject of sexual neuroses.

B. A. T.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
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The Inhibitory Action of Extract of the Posterior Lobe of the Hypophysis upon the Polyuria of Diabetes Insipidus.—George Eisner (*Deutsch. Arch. f. klin. Med.*, 1916, cxx, 438) reports two cases of diabetes insipidus which came under his care, and in which he had the opportunity to study the effect of extracts of the posterior lobe of the hypophysis cerebri upon the polyuria. He first reviews the literature, showing that opposite effects were claimed by different groups of workers. Von der Velden, Romer, Farnu, Hoppe-Seyler and others claimed that they had shown both in man and in animals that extracts of the posterior lobe inhibited diuresis, not only in normal individuals but in patients suffering with diabetes insipidus, and that, these results being true, diabetes insipidus must be considered as a hypo-activity of the posterior lobe of the hypophysis. On the other hand, Frank and Steiger differed, having failed to demonstrate any diminution in urinary secretion following the injection of posterior lobe extract. They, therefore, stated that on clinical, pathological and anatomical grounds diabetes insipidus must be considered as a hyperfunction of the neurohypophysis. Eisner's first case was that of a soldier, aged thirty-five years, who, shortly following a fall upon his head in the summer of 1914 which rendered him unconscious for five minutes, developed headache and shortly after that a greatly increased thirst and a polyuria. In November, 1914, he contracted pneumonia; convalescing from this, he resumed his soldier's life, and in February, 1915, was admitted to the hospital suffering from an intestinal condition suspiciously like dysentery. During his convalescence from this illness he acquired an acute gonorrhea and on

June 4, 1915, he was transferred to Eisner's care. At this time the patient was consuming 15 to 17 liters of fluid daily and passing 15 to 17 liters of urine, the specific gravity of which was not over 1 or 1.001. The only objective finding of any importance on physical examination was an intraspinal pressure of 220 mm. of mercury with the patient in the lateral recumbent position. His mental condition was rather euphoric, and headache at times was so severe that he could not wear his cap. Experiments were tried in an attempt to differentiate the type of diabetes insipidus present in the case, as Meyer claims that there are two varieties: (1) True diabetes insipidus, in which the kidneys are unable to secrete a urine of normal concentration, and in which the addition of sodium chloride causes an increased flow of urine without an increased concentration, and (2) a so-called "psychopathic" diabetes insipidus in which the concentration of the urine is raised after the administration of sodium chloride. Therefore, after patient had been on a constant diet, various amounts of sodium chloride, urea, dextrose and lactose were administered, all of them producing an increase in the specific gravity, and concentration of the urine with very little, if any, increase in volume of output. The phenolsulphonephthalein output, when the dye was administered intravenously, was 83 per cent. during the first hour. After these determinations had been made, various extracts (hypophysin, pituglandol) of posterior lobe substance were administered intravenously, intramuscularly and by mouth. The administration of these extracts was constantly followed by a short period of lessened urinary secretion, the urine excreted during this time having a higher specific gravity and increased concentration of NaCl and urea. However, the daily output was not diminished. A second case came under Eisner's observation shortly after this one. This case was a woman, aged fifty-eight years, who had a breast amputated in March, 1915, for carcinoma, an affection in which diabetes insipidus has rather frequently been described. In August, 1915, she noticed an increased thirst and augmented urinary secretion, amounting to 4 to 6 liters daily. She developed a progressive exhaustion and sleeplessness, frequent morning vomiting, and dryness of the mouth. Strychnin was injected without result and in October, 1915, she came into the hands of the writer. At this time the patient was large, well nourished but weak, with evidence of slight arteriosclerosis. Chest was negative and liver was slightly enlarged and firm. The scar on breast was healed, with no palpable lymph glands. Roentgenograms of skull showed multiple nodules in the skull. The urine averaged 4 liters per day, with a specific gravity of 1.002 to 1.005. Her health did not improve during her six weeks' stay in the hospital, and she died a few weeks after her discharge. In this patient the administration of sodium chloride resulted in a slight increase in the daily output of urine, while the specific gravity remained the same. About two-thirds of the salt was excreted in the same day, and the remainder on the following day. The experiments with urea did not give any definite results. The administration of hypophysin, however, gave distinct results in the urinary output for the day being distinctly lower, with increased specific gravity and higher concentrations of sodium chloride and urea. Eisner concludes from these experiments that extracts of the posterior lobe of the hypophysis will

diminish urinary secretion and increase the concentration and specific gravity of the urine in this group of cases of diabetes insipidus (with changes in the central nervous system) but that the effect is only temporary, and therefore these extracts cannot be regarded as an effective remedy. The value of the posterior lobe extract in diabetes insipidus must be as a diagnostic measure, for, if injections of the extract diminish the urinary output, and produce a urine that is normal or nearly so, the group of cases in which this result is obtained must be regarded as arising from diminished functionating of the posterior lobe of the hypophysis.

An Improvement of the Phenolphthalin Test for the Occult Blood in the Feces.—Boas (*Deutsch. med. Wchnschr.*, 1915, xli, 549) describes the modification of his recently proposed method of performing the phenolphthalin test for occult blood in the feces. The reagent is prepared as follows: 25 gms. of potassium hydrate are dissolved in 100 c.c. of distilled water, 1 gm. of phenolphthalin is added and the mixture is shaken vigorously. After solution is complete powdered metallic zinc is added and the preparation is boiled in an Erlenmeyer flask until the fluid is completely decolorized (two to three hours). After cooling, distilled water is added up to the original volume. Solution is filtered and the result is a water-clear solution, which remains colorless even after adding acetic acid, hydrogen peroxide and alcohol. The solution remains unchanged for several weeks. In the course of a few weeks oxidation of the phenolphthalin around the edge of the bottle may take place; this may color the first few drops of the solution pink and the bottle should therefore be wiped clean before using. The method of performing the test is as follows; an acetic acid-alcohol extract (5 drops of glacial acetic acid and 15 to 20 c.c. of alcohol) of the feces is prepared. From a dropping bottle 15 drops of the reagent are placed in a test-tube, to which are added 5 to 6 drops of 3 per cent. hydrogen peroxide and 2 c.c. of absolute alcohol. The tube is well shaken. The fecal extract is then run into the tube slowly so that it forms a layer. If blood coloring matter is present there appears either immediately or gradually a rose color or deep red ring at the line of contact. The depth of color depends on the amount of blood present. If the color is faint, it is more readily perceived by placing the tube before a white background. The result of the test is rarely doubtful but when such is the case the author proceeds in the manner devised by Schumm for increasing the delicacy of the guaiac test; the feces are rubbed with alcohol and ether in equal quantities in a crucible, filtered repeatedly and then the filtrate is evaporated to dryness. The dry residue is suspended in acetic acid-alcohol with the help of a stirring rod and filtered. Then the technic as described above is followed, when the ring becomes definite if blood is present. The author has compared the phenolphthalin test with the benzidin and guaiac tests and he has found the phenolphthalin test more delicate than the benzidin and much more sensitive than the guaiac. Whenever he has found the guaiac and benzidin tests positive the phenolphthalin test has been plainly positive. The observations described above relate only to the detection of blood in feces. For the detection of blood in the gastric contents this technic is not satisfactory as the author will show in a subsequent communication.

SURGERY

UNDER THE CHARGE OF

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Traumatic Aneurysm Dealt with by Obliterative Arteriorrhaphy.—JEFFERSON (*British Med. Jour.*, December 9, 1916, p. 794) reports a war case of true traumatic aneurysm in the left antecubital fossa, following a wound by a rifle bullet which gave little hemorrhage and healed within a few days. Two weeks after admission a pulsating swelling appeared and at the end of another four weeks it was the size of a hen's egg and was still increasing. A tourniquet having been applied to the arm the sac was laid open and the contained clots turned out. Three openings into it were discovered; one was small, situated on the inner aspect of the sac, and leading upward and backward. This was, probably, a common trunk of origin of the anterior and posterior ulnar recurrent arteries. Two larger openings in the lowest part of the sac were distant about $\frac{3}{4}$ inch from one another, and connected together by a deep groove. From them a probe passed upward and downward along the tracks of the brachial and ulnar arteries respectively. A probe sharply bent could be passed into the upper opening and then immediately downward along the course of the radial artery. Thus the condition was an aneurysm of the highest part of the ulnar artery. The interior of the sac was well scrubbed with iodine to promote adhesions, a continuous suture of fine chromic catgut on a fully curved intestinal needle was taken, and the smallest opening closed with four points of suture. In a like manner the upper opening was closed and the suture continued along the groove to close the lower opening. Following the recommendation of Matas, the sutures were made to enter the sac wall rather wide of the margins of the sides of the grooves. In this way was produced a firm approximation of as large a marginal surface as possible. The tourniquet was now removed and complete hemostasis seemed to have been secured. A second row of sutures was now inserted about half way up the walls of the sac. The skin flaps had not been dissected at all from the subcutaneous surface of the sac and so were lined with smooth sac wall. Two relaxation sutures were then introduced on each side to complete the obliteration and silkworm gut sutures brought the skin edges into apposition. Recovery was uneventful and the result quite satisfactory.

Comminuted Fracture of the Humerus Produced by Muscular Action.—MUMMERY and GIUSEPPI (*British Med. Jour.*, December 9, 1916, p. 795) reports the case of a soldier, aged thirty-three years, who sustained a comminuted fracture while throwing an empty hand grenade, in practice, which was about the size of a duck egg, made of steel, and weighed just over two pounds. He had raised the grenade up to and

behind his shoulder, as in the first position for "chucking it," as one would do in throwing a stone, and he did this suddenly and with a jerk. He felt his arm break, and it and the grenade, which had not yet left his hand, dropped. The officer in charge and several other men, saw the accident happen, and there is no question as to this having been the exact method of its occurrence. The patient was an exceedingly muscular man, with thirteen years' service, who had never had any serious illness nor previously broken a bone. The roentgen-ray, operation, and a postmortem, a month and a half after the operation, showed the comminuted fracture.

Flavine and Brilliant Green.—Browning, Gulbransen, Kennaway, and Thornton (*British Med. Jour.*, January 20, 1917, p. 73), working in the Bland-Sutton Institute of Pathology, the Middlesex Hospital, say that they have, in the course of the past year and a half, examined an extensive series of substances, comprising the principal antiseptics in common use and also other compounds, some of which have not hitherto been recognized as antiseptics or applied as such. A substance belonging to the acridine group, flavine, has been found to possess extremely powerful bactericidal and antiseptic properties, which are enhanced rather than diminished by admixture with serum. In this respect flavine differs from all the powerful antiseptics in common use. In the presence of serum, flavine is the most powerful bactericide of all those investigated for both Staphylococcus and B. coli, and it is equally efficient for the enterococcus and for anaërobes such as B. edematous maligni. Flavine, in relation to its bactericidal power, is very much less detrimental to the process of phagocytosis and less harmful to the tissues than the other substances; hence much higher effective concentrations can be employed without damaging the tissues or interfering with the natural defensive mechanisms. Brilliant green also compares most favorably with the other antiseptics in these respects. Clinical results have substantiated the estimate of the therapeutic value of flavine and brilliant green based on the characters above noted. The duration of septic conditions is in general reduced to at least a half, the stimulus to connective tissue to form granulations is a very outstanding feature, and these antiseptics can be applied in considerable amounts with the minimum of interference with the normal tissue functions. As regards the comparative merits of brilliant green and flavine, the latter is considered both the more efficient and the more rapid in action.

Flavine and Brilliant Green in the Treatment of Infected Wounds.—Ligat (*British Med. Jour.*, January 20, 1917, p. 78) says that for over a year he has employed flavine compounds and brilliant green in septic cases under his care in the Middlesex Hospital. Upward of 150 cases have been treated, about 50 per cent. of these being war wounds. In the case of suppurating wounds the procedure followed has been to secure adequate drainage by free incision when necessary, and then to irrigate with a 1 to 1000 solution of the antiseptic in normal saline, finally the wound is covered with gauze soaked in the solution, and protective applied to prevent evaporation. Where there has been a cavity it has been packed lightly with gauze soaked in the solution. A considerable diminution of the discharge of the pus may be expected

at the end of twenty-four hours. In wounds of moderate severity in which no foreign body is present and in which free drainage is secured, the suppurative process may be expected to come to an end after four or five days' treatment. From the few cases in which there has been an opportunity to apply the antiseptic before the evidence of sepsis has appeared it is considered that the results of the highest value are to be anticipated in the future by what one may term the "prophylactic" use of these antiseptics. Ligat has used considerable quantities both of brilliant green and flavine over prolonged periods; in some cases he has no hesitation in injecting the latter antiseptic into the tissues, and he has never observed any toxic phenomena following their use. Of the two antiseptics investigated he has found flavine to be the more efficient, especially in heavily infected wounds with free discharge of pus, and he now uses this antiseptic exclusively for septic cases. He regards these substances as satisfying therapeutic requirements for the treatment of wounds in a manner superior to any of the antiseptics hitherto employed.

The Bacteriology and Microscopy of the Contents of the Seminal Vesicles Postmortem. A Study of Fifty-two Cases.—THOMAS and HARRISON (*Jour. Urol.*, 1917, i, 50) say that in view of the unprecedented interest manifested by urologists today in spermatocystitis, and in realization of the focal sepsis occasioned thereby, too little suspected and investigated by the average medical man, but nevertheless characterized by a retinue of urinary, arthritic, neurological, mental and even systemic diseases, it behooves the profession to welcome any attempt to study this obscure affection. Some investigators regard spermatocystitis as the commonest complication of gonorrhea. It is probably true that epididymitis does not exist without an associated seminal vesiculitis, and the belief is gradually gaining credence that inflammation of the spermatic vesicles is as common, if not more frequent than prostatitis, as a gonorrheal complication. Mayer found 60 per cent. of patients with posterior urethritis to have involvement of the seminal vesicles. Lewin and Bohm encountered spermatocystitis in 35 per cent., and prostatitis in 29 per cent. of 1000 gonorrheal cases. The particular purpose of the writers is to establish on a firmer basis certain indefinite and conflicting ideas concerning: (1) the presence of spermatazoa in the seminal vesicle, (*a*) normally and (*b*) when inflamed; (2) the life or death of spermatazoa in spermatocystitis and (3), the indentification of the invading bacteria, gonorrheal and non-gonorrheal. They concluded that the seminal vesicles harbor spermatozoa after death, and therefore presumably during life. This function is exercised in the presence of inflammation (spermatocystitis), although in a large percentage of inflammatory cases no spermatozoa can be found (postmortem). The determination of the viability of the zoösperm in the presence of the seminal vesiculitis, the exact identification, classification and relative frequency of the invading bacteria, particularly with reference to gonorrhea are questions impossible of solution by postmortem investigation.

THERAPEUTICS

UNDER THE CHARGE OF

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The Nature of Pneumonia and the Serum Treatment.—Cole (*New York Med. Jour.*, 1917, cv, 233) from a study of pneumonia at the Rockefeller Institute, reports that most cases of pneumonia are caused by pneumococci which can be divided into at least four types. Over 500 cases of pneumonia have been studied for the purpose of determining the relative frequency of the different types of infection. The results showed that 60 to 65 per cent. of all cases were due to pneumococci of Types I and II, while 10 to 15 per cent. were due to pneumococci of Type III, the remaining 25 per cent. being due to pneumococci belonging to Type IV. Studies were also made to determine the frequency of occurrence of the different types in mouths of normal persons. In examinations of 527 people, 254, or about half, showed pneumococci. They belonged to the Type IV group in 75 per cent. In 17 per cent. the pneumococci were of the Type III group, while in less than 12 per cent. they were of the so-called fixed Types I and II. In practically all the instances in which organisms of Types I and II were found in normal mouths, it was possible to trace a close relationship between these individuals and a case of pneumonia of the same type. Pneumococci of Types I and II tend to disappear from the mouth in a short time as after convalescence from pneumonia. The author believes that isolation of cases of pneumococci of Types I and II should be more strictly observed than is the usual practice. With the present knowledge it was not possible to have an opinion on the value of isolation of cases due to pneumococci of Type III. Probably no effect would be obtained by isolation in cases of infection with Type IV. With regard to specific treatment the author believes that vaccine treatment is without much beneficial effect. He has made use of serum prepared from animals made immune to organisms of the different types. He notes that on account of the specificity of types it is necessary to determine the type of infecting organism in each case before instituting serum therapy. This determination of type of organism is of important prognostic value. The author has used immune horse serum prepared against the three important Types I, II, and III. The serum against pneumococci of Type I was of high power, that of Type II was considerably less powerful while that of Type III had very little effect, either in the test-tube or on experimental animals. So far no attempts have been made to use the serum on patients with Type III infection. A limited trial has been made with serum against pneumococci of Type II, but the results have not been promising. The use of immune serum against infection with organisms of Type I, however, has given very gratifying results and experience indicated that with proper

use this serum had great therapeutic value. In the hospital of the Rockefeller Institute, 78 cases were treated with 6 deaths. The mortality was 25 per cent. in cases due to Type I infection, before the serum was used, so that it was evident that the serum was of considerable value. Of the 6 fatal cases, 1 died on the fifty-third day following pneumonia from general streptococcus infection; 1 died during convalescence from pulmonary embolism; 3 were treated only on the day of death late in the disease, leaving but 1 fatal case that received treatment over two days. In order to obtain the best results certain rules must be observed. First, serum must be given in large amounts intravenously, and its administration must be commenced as early in the disease as possible; its use must be continued until infection was definitely overcome. Before administering the serum a small dose of normal horse serum should be given subcutaneously in order to desensitize the patient in case he was sensitive to horse serum. Among the treated cases the evidence of empyema has been greater than in the untreated cases. This probably meant that in a large number of the cases, otherwise fatal, the infection was localized instead of becoming general.

A Report on the Treatment of Pernicious Anemia by Transfusion and Splenectomy.—Giffin (*Jour. Am. Med. Assn.*, 1917, lxviii, 429) says that there is no evidence that splenectomy has cured pernicious anemia. A review of 31 cases of splenectomy for pernicious anemia demonstrates a definite gain in the blood, the weight, and the general condition during the first three months of the postoperative period in 78 per cent. of the cases; during the second three months' period, 68 per cent. of living patients maintained their gain. A consideration of the advisability of splenectomy would seem to be warranted at present chiefly in young and middle-aged patients of good general resistance, who show evidence of active hemolysis and in whom the spleen is moderately enlarged. The estimation of the blood-derived pigments in the duodenal contents is valuable in determining the degree of hemolytic activity present at a given time. A comparison of the degree of hemolysis with the severity of the anemia would seem to be indicative of the productive power of the bone-marrow. Preoperative treatment, especially transfusions, should be employed to influence the general condition of the patients and to improve the characteristics of the blood picture. The operative risk is increased when the hemoglobin is below 35 per cent. and the erythrocyte count less than 1,500,000 cells. Postoperative transfusions have not been given as a routine procedure, but transfusions have been successfully employed in postoperative relapse.

The Treatment of Tuberculous Pericarditis by the Induction of an Artificial Pneumopericardium.—Weil and Loiscleur (*La Presse Méd.*, 1916, xxiv, 601) recommend the introduction of air into the pericardial sac after paracentesis of a pericardial effusion by employing a similar technic as in treating a pleurisy with effusion by artificial pneumothorax. They cite a case treated in this way with the treatment controlled by frequent roentgen-ray examinations. They believe that adhesion of the pericardial layers can be prevented

by this procedure, and preëxisting adhesions are generally broken up by the introduction of the air. The pericardial sac in the case treated by the authors continued to refill but the intervals between tappings became progressively lengthened from eight to fifteen to thirty-three to forty-eight days. The injection of air in an amount equal to that of the fluid removed caused no untoward effects; no pain, no dyspnea, no symptoms referable to the heart itself were produced.

Home-made Bread Substitutes for Diabetic Patients.—Nicholson (*British Med. Jour.*, 1917, 2925, 82) recommends a bread made of peanut flour and casein. It has the advantage of being very nice to the taste, and can be cut readily into slices, even as thin as white bread. The formula for making it is as follows: Peanut flour, 8 ounces; casein, 2 ounces; a pinch of salt; white of eggs, 12 ounces. The white of egg is beaten to a snow, and then the other ingredients (previously lightly mixed) are slowly added.

Disappearance of Malignant Tertian Crescents from the Blood following the Intravenous Injection of Tartar Emetic.—Rogers (*British Med. Jour.*, 1917, 2923, 6) who has already reported success in the cure of kala-azar by tartar emetic intravenously, tried the same drug in the treatment of patients with persistent malarial crescents in the blood. He says that it is well known that once crescents appear in the blood they remain present for months uninfluenced by quinin, and cites the details of 4 cases treated by intravenous injections of tartar emetic with rapid disappearance of the crescents from the circulating blood. The author is not too sanguine but suggests the more wide-spread use to determine its value. He says that much further experience will be required to settle these points but the indications to be derived from these few cases appear to be that quinin should be used to check the malarial paroxysms, while tartar emetic should subsequently be given intravenously, in the hope that it may prove of value in destroying the extracorpuscular stages of the malarial parasites and so prevent relapses and greatly lessen the infectiveness of the patient to malaria-bearing mosquitoes by killing the crescents of the malignant tertian variety and the corresponding resisting forms of the other types of malaria.

Home-made Bread Substitutes for Diabetic Patients.—Williamson (*British Med. Jour.*, 1917, 2921, 870) gives formulas for home-made bread substitutes which have been of great service to him in his care of diabetic patients. The following formula is a sample upon which a number of different combinations are based. Formula: Soluble casein, 3 tablespoonfuls; gluten flour, 2 tablespoonfuls; baking powder, ½ teaspoonful; 1 egg well beaten; small pinch of salt. Mix well together, adding the baking powder last. A little water may be added if necessary. Drop into six tins and bake twenty minutes. Formulas are also given for various combinations of the soluble casein with cocoanut powder and almond flour with and without gluten. He advises that diabetic patients should not try one bread substitute only but they should try several until the most palatable is obtained for the individual patient.

PEDIATRICS

UNDER THE CHARGE OF

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Communicability of Poliomyelitis.—KERLEY (*Arch. Pediat.*, 1917, xxxiv, 32) offers interesting observations bearing on the questions of the transmissibility of the disease by the diseased to the unprotected individual by human contact; the part played by the innocent in the transmission of the disease, and the proportion of healthy children who are susceptible. The following facts have a striking relation to transmission by human contact: There were no cases of the disease on Governor's Island, New York, during the recent epidemic. There are about 80 children on the island, and a strict quarantine of children under sixteen years was maintained throughout the epidemic. There were no cases on Barren Island, with 350 children, in a population of 1500 people. The geographical and social isolation of this community can be considered responsible for its immunity from the disease. Among the 21,746 children in 93 institutions under permanent jurisdiction of the Health Department of New York City, but 10 proved cases developed. Three of these developed within two weeks of their admission to the institutions and three others were allowed to mingle with city children in a public park. This low morbidity is to be ascribed to the strict quarantine established in these institutions by the Department of Health. The conclusion being safe that the disease would spread along the lines of human travel to isolated sections, the author thoroughly investigated a number of first cases occurring in isolated communities in northwestern Connecticut, in which the disease had not been known to exist for a period of ten years. He reports 11 cases of the disease under the above conditions, and in almost all the cases it was proved that some person coming from an infected locality had come in contact with the case just previous to its development, the infection being borne by the innocent carriers. In 2 cases the disease was transmitted by coming in personal contact with children recently arrived from an infected locality who were at the time or quite recently ill from a condition not diagnosed as poliomyelitis but which was later shown to have been that disease in its abortive form. The author concludes as reasonable that poliomyelitis may be communicated through personal contact and that there are innocent carriers who spread the disease. Also, that but a small percentage of children are susceptible to the disease and that probably from 90 to 95 per cent. possess an immunity.

Some Clinical Aspects of Anterior Poliomyelitis.—MARTIN (*Canadian Med. Assn. Jour.*, 1917, vii, 113) states that recent observations and researches of this disease demonstrate the need of reconstructing our ideas of it. Epidemics show that even the very large

proportion of the cases are not accompanied by paralysis. The disease appears to affect all ages and classes. It is essentially infectious and communicable, the virus apparently entering the body through the mucous membranes of the nose, throat, and intestines, and affects chiefly the nervous system. The mode of infection is undoubtedly by personal contact, and convincing evidence has demonstrated that no intermediate way exists. Flies and domestic animals do not communicate the disease except as passive carriers. Healthy, contaminated persons can carry the virus through the secretions of their mucous membrane. Many people have a natural immunity to the disease. The average incubation period is eight days. The prodromal stage if present shows indefinite body pains, fatigue and pressure or aching of the head. The onset shows a high fever of short duration and usually ending by lysis. The general symptoms are headache, vomiting, constipation, pains generally over the body but particularly in the nape of the neck. Stiffness of the head and neck, refusal to flex the chin on the breast. Hyperesthesia is characteristic and, as a rule, diffuse. Weakness, with flaccidity of the muscles, and drowsiness are characteristic symptoms. These symptoms may last from five to ten days followed by rapid recovery, when the case is termed "abortive." However, recurrence may follow with a subsequent paralysis. The various types of the disease are described, depending on the anatomical lesion in the nervous system. The abortive type comprises 35 to 56 per cent. of all cases, and is the most dangerous form from the point of dissemination of the disease. During epidemics every person with an acute infection is rightly to be regarded as a suspect.

Early Diagnosis of Pott's Disease.—Taylor and Darling (*New York State Jour. Med.*, 1917, xvii, 51) impress the value of habitually thorough examination of children in illness in avoiding errors in diagnosis of this disease. Pott's disease is essentially a disease of childhood, 90 per cent. of cases occurring before the fifteenth year. It is desirable, if possible, to make a diagnosis before destruction of vertebræ or surface abscess formation occur. The disease develops more rapidly in children than in adults and abscess or deformity may appear in a few months. Among the earliest signs of the disease in childhood are general debility, slight anemia, failure to gain, lack of interest in play, tendency to lie down often, unnatural attitude, change in gait, night cries or paroxysmal abdominal pain or persistent attacks of pain in the chest or stomach. The child moves cautiously, leans on a table or chair at every opportunity and tends to walk on toes. These symptoms are suspicious. On inspecting the spine, if the lesion is cervical there may be unnatural posture of the head or supporting the chin with the hands when sitting. The most usual location of the lesion in children is the dorsal region and with this situation may be found elevation of one or both shoulders, rigidity of the spine when walking and placing the hands on the thighs to support the spine when sitting. A slight lateral curve may be seen. If the disease is lumbar there is exaggeration of the normal curve which throws the abdomen forward and the child characteristically squats instead of stooping to pick up an object. It may be possible to detect approximation of two vertebra

when the spine bends or interruption of the normal curve of the spine when the child leans forward. Waterman and Yager in an analysis of 1000 cases found the most frequent early signs in young children to be the unnatural attitude and the pain and muscular rigidity.

GYNECOLOGY

UNDER THE CHARGE OF

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Radium Treatment of Cervical Carcinoma. — Reports upon this subject are now becoming quite common in the American literature, showing that numerous clinics are giving it a trial, and while these reports for the most part are as yet distinctly preliminary in nature, and cover small series of cases, they are of interest in showing the development of the technic and applicability of the treatment. In a recent report FRANK (*Jour. Cancer Research*, 1917, ii, 85) says that he has had put at his disposal 130 mgs. of radium, contained in four tubes, the largest holding about 80 mgs., and the others smaller amounts. For the treatment of small carcinomata, where concentration of the rays is desirable, he has devised a hollow lead cup on the end of a long handle of stiff wire. The uncovered glass tubes, containing the radium, are put in this cup, which is then closed with a brass lid held in place by adhesive, and the whole covered by a small rubber bag 1 mm. in thickness to cut out the secondary rays. Thus all the rays are blocked in all directions but in the one in which it is desired to have them act. For larger cauliflower growths, the chief radium tube is placed in a brass capsule 1.5 mm. thick, which is screwed to the end of a long wire handle. If a larger dosage than this affords is desired, the additional tubes are fastened around the periphery of the first with adhesive, and the whole then covered with a rubber bag and introduced together by means of the handle. In crater-like carcinomata the central tube is advanced a couple of centimeters ahead of the three smaller ones, thus permitting its introduction into the cervix, the smaller tubes at the same time radiating the vaginal portion and fornices. If it is desired to screen one side, this is done by introducing four to eight thicknesses of lead foil inside the rubber bag. Unless the carrier is to be introduced actually inside the cervical canal a layer of gauze is interposed between it and the growth. The carrier is always introduced by sight after retraction of the vaginal walls; it is pushed firmly against the gauze by means of the handle, and the vagina is then tightly packed with gauze so that its walls are separated as far as possible from the radium. The handle remains sticking out of the vagina, and is secured to the vulva by means of strips of adhesive. The radium is usually allowed to remain in place eighteen to twenty-four hours; the frequency of

application depends largely upon the reaction (pain, rectal and vesical tenesmus, symptoms of absorption or toxemia). The usual routine followed by the author is to give a second treatment seven to ten days after the first, and if improvement is apparent two more at intervals of three weeks with diminishing dosage, applying in this first series a total of 5000 to 6000 milligram hours. Thereafter one treatment each month completes the primary treatment; the patient presents herself at least once a month, and if a recurrence manifests itself a new series of radiations is undertaken. Frank has followed most of his cases by the microscopic study of excised bits of tissue from time to time, and has found the usual cell changes that have been often described. The limit of penetration of direct action of the radium appears to be about 1.5 cm., but the author believes that cancer cells may be destroyed beyond this zone by the strangling action of the contracting connective tissue, which is greatly stimulated by the radioactivity. In one instance, a uterus the seat of a well developed squamous carcinoma of the cervix was removed by radical operation seven weeks after the beginning of treatment and cut in serial sections, but only two very small suspicious areas of malignancy could be discovered. In common with all other careful observers, however, Frank warns against forming false hopes of permanent cures in these cases, and considers that all we can say of radium at present is that it is the best palliative—though only a palliative—treatment for inoperable cases of cervical cancer.

Significance of Hematuria.—An interesting analysis of 238 cases of hematuria has been made by KRETSCHMER (*Jour. Am. Med. Assn.*, 1917, lxviii, 598), who very properly calls attention to the great importance of this symptom, since with very few exceptions it means organic disease in the urinary tract, and yet it is very often disregarded and belittled by both patient and physician. It is often unaccompanied by pain, and as the exact location of the trouble is usually difficult of determination, various styptic drugs are administered, while both patient and physician *wait* for the bleeding to stop. The fact that a large percentage of these cases are in reality due to new growths or tuberculosis of the kidney, conditions in which early treatment is of vital importance, should indicate the necessity for making an early, accurate diagnosis. Of the 238 cases studied by Kretschmer, an accurate diagnosis was made in 197. In 74 of these the trouble was in the kidney, the list of lesions being headed by tuberculosis and nephritis, with 23 and 12 cases respectively. Next in order of frequency came renal calculus, hypernephroma, and colon-bacillus infection, with 8 cases each, then carcinoma, other renal tumors, polycystic disease, trauma, and hydronephrosis, with 2 cases each. Pyonephrosis, movable kidney, pregnancy, doubtful stone, and oxaluria each accounted for a single case. The bladder was the seat of the hemorrhage more often than the kidney, being involved 86 times. The largest number of these cases, 36, were due to carcinoma; papilloma was responsible 26 times, calculus 14 times, and vesical tuberculosis 10 times. There were two cases of diverticula, and one each of angioma and polypi. The prostate was the source of the hemorrhage in 25 cases in males, ureteral calculus was the factor 10 times, and prolapse and tumor of the female urethra once each. Taking the series as a whole, tumor formation in some portion

of the urinary tract was distinctly the most frequent cause of hemorrhage, followed by tuberculosis and calculus. In many of these cases, it was necessary to study the patients over considerable periods of time, and to make numerous and varied examinations, before the true condition was determined. Kretschmer says that he makes it a rule to inject guinea-pigs routinely in all cases of obscure hematuria, as it is at times impossible to demonstrate tubercle bacilli in the sediment of urine containing a large amount of blood. In the remaining cases of the series, the source of the hemorrhage but not its cause was determined in about a third. Most of those in whom neither the origin nor the cause could be determined either refused instrumental examination, or for some reason this could not be carried out. In only 6 cases of the entire series in which complete examinations were made was no light thrown on the condition. In these, cystoscopic examination, ureteral catheterization, cultures of the urine, roentgen-ray examination and pyelography were all completely negative. The author does not consider these cases of so-called "essential hematuria," but merely expressions of our present diagnostic limitations, and thinks they should be subjected to further clinical observation.

Gangrene of the Uterus following Criminal Abortion.—Mauclaire (*Ann. de gynéco. et d'obst.*, 1916, xlii, 193) calls attention to the fact that serious and often fatal symptoms may arise following the introduction of irritating solutions or unclean instruments into the uterus due to gangrene of the wall of the fundus, associated with a small area of perforation, or even in the absence of any perforation. He cites 4 cases, in 2 of which no perforation has occurred primarily, though in one of these a large perforation in the fundus, due to gangrene, was found in the uterus removed at autopsy twelve days after an exploratory operation, at which the peritoneal covering of the uterus was found to be intact, with a recognized subperitoneal area of beginning gangrene, the uterus, however, not being removed at that time. In the second case, two spots of subperitoneal gangrene, at the tubal angles, with intact peritoneum, were recognized at operation and the uterus removed; microscopic examination verified the diagnosis. In all these instances, the gangrenous area is more or less conical in shape, with the apex in, corresponding in outline to that of an infarct, a condition that is explained by the anatomical relationships of the terminal vessels in the fundus. Leclerc and Crispin have shown by injection experiments that in the fundal region the terminal arteries approach the intertubal line without anastomoses, differing in this respect from the vascular arrangement in the corpus and cervix. The fundus is therefore in a poor condition for defense against vascular lesions, and an infection in the uterus causing thrombosis of one of these little terminal arterioles may easily lead to the formation of a gangrenous perforation even though no actual mechanical perforation was caused at the time of the instrumentation. This fact emphasizes, in Mauclaire's opinion, the necessity for the most careful watching of these cases, and the performance of an immediate laparotomy upon the first vestige of peritoneal symptoms, even if it appears exceedingly unlikely that the preceding manipulations had actually resulted in perforation of the uterine wall.

OBSTETRICS

UNDER THE CHARGE OF

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Ophthalmia Neonatorum.—The frequency and prevention of this disorder are considered in the public health report of the city of London, on which an abstract is made in the *British Med. Jour.*, September 16, 1916. 537 cases during a year were investigated, of which 456 completely recovered. In 6 there was permanent impairment of vision, in 1, definite history of gonorrhea in both parents, and both eyes of the child were affected from the moment of birth. Instructions were given to take the child to the hospital for treatment, but this was not done, and the child became blind in both eyes. Among the mothers there was a history of vaginal discharge in over one-third of the cases, 39.6 per cent. Among the children having ophthalmia 20 died while suffering from the disease. In 53 cases the parents took the child from observation before a definite termination of the case had occurred.

Lumbar Puncture in the Fetus.—Costa (*Jour. Ann. di Ostet.*, No. 6, 1916) discusses the problem of lumbar puncture upon the fetus in cases of breech presentation where birth is difficult because of contracted pelvis in the mother, or excessive development in the child. He described a case of contracted pelvis with a conjugate avara 7.4 cm. in which lumbar puncture was done upon the fetus in breech presentation, resulting in the spontaneous expulsion of a female child weighing 3200 gm. and 50 cm. in length. The fetus died on the fourth day after birth from general debility, and a careful examination failed to disclose any injury to the nervous system resulting from the lumbar puncture. Other similar cases are cited, and the conclusion of the writer is that this method has a distinct field of usefulness, especially in cases in which there is moderate pelvic contraction.

Rupture of the Scar of a Previous Cesarean Section.—Findley (*Am. Jour. Obst.*, September, 1916) has collected 63 cases in which rupture of the uterine scar has occurred in patients upon whom previously Cesarean section had been performed. The analysis of these cases shows that a perfectly healed scar may be relied upon to resist the force of labor, but as one cannot tell what happens to the Cesarean wound after operation in most cases, every precaution must be taken to secure accurate and aseptic union. The principles of suture produced by Sänger which call for the accurate closure of the uterus muscle separately, followed by closure of the peritoneal covering of the uterus, must be strictly followed. A second important factor is absence of infection. There may be present a latent gonorrheal infection which may defeat the most careful efforts to secure a perfect healing. When after Cesarean section the patient's convalescence has been complicated

by fever, this must be regarded as a sign that the wound in the uterus is not properly healed, and should such a patient come into subsequent labor, she should be delivered by section at the onset of labor. In all cases of labor where infection is known to exist, and the necessity for section arises, sterility and hysterectomy should be performed, and not the ordinary conservative section. Transverse, fundal, extraperitoneal and cervical incisions have not lessened the liability of rupture in the uterine scar, but have probably increased it. In cases of Cesarean section the danger of subsequent rupture of the scar is not so great that each Cesarean section should be followed by sterility. Patients who have had section and who subsequently become pregnant should be delivered in a hospital with skilled attendance where operation could be promptly performed if necessary. Version, high forceps, tamponing the uterus, the use of bags, and the giving of pituitrin should never be employed in patients who have a Cesarean scar. Not more than 2 per cent. of cases delivered by section have a rupture of the scar in subsequent labor, and this shows that the argument "once a Cesarean section always a Cesarean section" is not reasonable. There is, however, sufficient danger to forbid the indiscriminate use of the Cesarean operation.

A Practical Method of Estimating the Condition of the Ovaries.—In an article upon fertility and sterility, REYNOLDS (*Jour. Am. Med. Assn.*, October 21, 1916) draws attention to the fact that at operation practical idea of the condition of the ovaries may be obtained by a careful palpation. The consistence of the normal ovary is distinctly soft and elastic and uniform. One of the most frequent pathological processes found in the ovaries is sclerosis, and this can be appreciated better by touch than even by sight. The decision to remove or leave an ovary in a given case may often be properly made by careful palpation of the ovary, and the recognition of a considerable area which is normal in consistence. Where, on the other hand, nothing but firm sclerotic tissue is present the ovary is in all probability incapable of function.

Rupture of the Uterus following the Use of Pituitrin.—MCNEILE (*Am. Jour. Obst.*, September, 1916) reports the case of a strong-looking Mexican woman who had three labors previously, two terminated by the use of forceps and one spontaneously. The position and presentation in the fourth labor were normal and favorable, and as uterine contractions grew feeble during labor, pituitrin was given. This was immediately followed by tetanus of the uterus with pain in the epigastric region and chest. Uterine contractions ceased. Later the patient was delivered of a stillborn child. Hemorrhage followed and when the hand was introduced into the uterus to deliver the placenta it was found in the abdominal cavity. On admission to the hospital the patient was semicomatose, and on section a transverse rupture of the lower segment was found, the edges of the tear badly lacerated. A supravaginal hysterectomy was done with drainage; the patient recovered. On subsequent examination the pelvis was obliquely contracted. In the literature including his own, the writer has collected 16 cases of rupture of the uterus following the use of pituitrin, with thirteen deaths. After considerable experience with the drug the con-

clusion is that pituitrin has absolutely no place in normal obstetrics, and in selected cases only, under accurate observation and skilful care, is its use permissible. The reviewer has recently seen a case where separation of the placenta followed the administration of pituitrin; also a case of contracted pelvis where pituitrin was given repeatedly, and forceps used unsuccessfully, and a case of uterine rupture following the use of pituitrin. This substance is probably the most dangerous drug at present in the hands of the general profession.

Spontaneous Rupture of the Uterus.—TELFAIR (*Am. Jour. Obst.*, September, 1916) reports the case of a patient admitted to hospital in shock, with breech presentation in which the fetus could not be safely delivered by traction. On opening the abdomen a transverse rupture across the vaginal vault was found opening up the broad ligament on the left side and extending up upon the uterus. Craniotomy and extraction were immediately performed followed by hysterectomy. The patient did not survive the operation. In discussion a case was described in which after a perfectly normal and rapid labor a patient had died from profuse hemorrhage behind the peritoneum arising from a tear in the left broad ligament which had opened the uterine artery. It also developed in discussion that a spontaneous rupture of the uterus can occur as low as the broad ligaments without interference during labor.

Pregnancy following Extensive Operations upon the Pelvic Organs.—VINEBERG reports a case where a gangrenous appendix was removed, also one tube and ovary, and adhesions around the other tube freed, and the opening of the closed tube resulted, the ovary remaining. Although the operation was a difficult and extensive one, the patient made a good recovery and subsequently became pregnant. Speaking from clinical experience there seems to be no condition in the abdomen so complicated by adhesions that pregnancy may not occur if ovarian tissue be left and one tube which is in any degree patent.

The Transmission of Hereditary Syphilis.—GAUCHER (*Bull. de l'Acad. de méd.*, September 26, 1916) reports the case of an apparently healthy young couple free from acquired venereal disease who had three children presenting the manifestations of inherited syphilis of a severe type. One child is an idiot. Gaucher had been the physician of the grandfather, and remembered that although this man had never acquired venereal disease, that he had hereditary syphilis. He died in early manhood from syphilitic paraplegia. This interesting case illustrates the potency of hereditary syphilis even to the fourth generation.

Puerperal Eclampsia.—SCHEULT (*Jour. Obst. and Gynec. Brit. Emp.*, June–August, 1915) gives the results of his operations on 122 cases of puerperal eclampsia in the hospital at Trinidad. His observations show that in the majority of cases nephritis was present in varying degree. The greater number of these cases were primiparæ and the influence of twin pregnancy is recognized in causing eclampsia. The disease seemed less frequent when the weather was driest and the coming of the rainy season was followed by an increase in the number of cases. The maternal mortality was 22.9 per cent. and the fetal mor-

tality was 34 per cent. Three cases after recovery had marked mental disturbance and had to be treated in asylums. Four patients recovered from eclampsia without coming into labor, three of whom went to full term and one was delivered prematurely. In one case a full term, well-developed child developed eclampsia convulsions seventeen hours after birth, which proved fatal.

OTOLOGY

UNDER THE CHARGE OF

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The Pathology of Otosclerosis.—By J. S. Fraser and R. Muir (*Jour. Laryngol., Rhinol., and Otol.*, vol. xxxi, No. 11).—This communication, a part of the report for the year 1915 from the ear and throat departments of the Royal Infirmary at Edinburgh, is a valuable contribution to the record of the pathological facts and an inferential study of the etiology of the several forms of tissue change in the middle ear or labyrinth, which have been grossly included under the title name of this communication, and includes various references to the literature of the subject and suggested explanations of the concomitant symptoms, the paper moreover being richly illustrated by plates of microscopic sections. The theories as to the pathology of otosclerosis fall under four headings: That it may be congenital; that it may follow inflammatory changes in the middle ear; that it may be due to infection through the blood; and that it may be caused by abnormal conditions in the nerve supply of the parts affected. (1) According to the first theory, otosclerosis is a congenital anomaly of the process of growth in the petrous portion of the temporal bone, due to the presence of certain determinants in the patient's blood. This anomaly only becomes manifest after puberty. (2) Otosclerosis is regarded by some as a chronic inflammatory process spreading from the mucoperiosteum of the middle ear and following attacks of catarrhal or suppurative otitis media. The inflammatory condition is supposed to linger about the niche of the oval window and to invade the bone from the deep layer of the mucosa. Such an invasion may be favored by the anastomosis which occurs at this spot between the tympanic vessels and those of the bony labyrinth capsule. Further, as has been pointed out, the joints in the middle ear are the only articulations in the body covered by mucous membrane, and therefore liable to infection from the surface. (3) A third group of otologists look on otosclerosis as a primary disease of the bone, the infection coming by the way of the blood-stream, as in osteomalacia, rheumatism, etc. Ferreri regards otosclerosis as closely allied to osteomalacia, and finds that almost all patients suffering from the latter disease are also the subjects of otosclerosis. A variant of this view is held by A. A. Gray, who has put forward the theory that otosclerosis is an aseptic

necrosis of certain areas in the labyrinth capsule—apparently as a result of aseptic infarction. Gray believes that similar areas occur in other bones of the skeleton. (4) Lastly otosclerosis is regarded by a small group of observers as due to a trophic disturbance—*i. e.*, as a degenerative atrophic process. According to this theory the changes (sometimes) found in the ganglia and nerves are primary, while those in the labyrinth capsule are secondary. In this connection it may be noted that certain cases, which clinically appeared to be examples of *nerve deafness*, on microscopic examination showed spongification of the labyrinth capsule with (Siebenmann) or without (Bruehl) ankylosis of the stapes. This type of otosclerosis associated with nerve deafness—the so-called "atypical otosclerosis"—is markedly hereditary. The author of the second part of the paper gives a compact statement of the pathologic changes as determined under section and microscopic observation, and points to the fact that the study of sections from cases of otosclerosis strongly suggests the structural changes met with in other bony tissues in conditions of chronic toxemia or altered metabolism. Whatever be the exciting cause of this condition we have a series of progressive changes which appear to be *purely inflammatory* in character. The ultimate result is a typical and constant lesion, viz. marked sclerosis of the bony tissue of the labyrinth capsule. The alleged absence of plasma cells does not prove that otosclerosis is of non-inflammatory origin. These cells are not present in all forms of chronic inflammation. Even when they are present they do not occur in all stages of the inflammatory process. For their detection special staining methods are required—methods difficult to apply to celloidin sections of the labyrinth. The first change one observes in otosclerosis is the marked and general engorgement of the bloodvessels both in the fatty marrow of the bone and in the mucoperiosteum. The connective tissue of these areas is also seen to increase in amount, having a loose, open, and fibrillated structure. There are more cellular areas, mainly composed of mononuclear cells, which are closely related to the congested vessels. Some of the medullary spaces in the petrous bone show leukoblastic marrow reaction. Such appearances can be explained by a toxic body brought by the blood or stimulant, especially on the connective tissues of the marrow. The condition is essentially a granulating process, which slowly brings about absorption of the bone, allowing the opening up of the medullary spaces. The deeply staining bone seen around the enlarged medullary spaces appears to be old bone which is undergoing change, and not new-formed bone, as described by various writers. The granulation tissue tends to become more fully formed fibrous tissue, and these fibers range themselves in concentric layers around the central vessel. Ossification of this fibrous tissue now sets in, beginning with the fibers lying in close relation to the bone trabeculæ, thus bringing about a marked thickening of the lamellæ at the expense of the Haversian canals. The inner layer of the bone in the labyrinth capsule also appears to be involved in this process of sclerosis. There is an active proliferation of the cartilage cells and ossification into a bony matrix.

The above changes seem to be of a patchy character and appear to begin at the junction of the cartilaginous and lamellar portions of the labyrinth capsule, and to spread directly along that line for some distance, extending more or less into the cartilaginous and lamellar bone

on each side, and in places passing right through the cartilage bone to reach the endosteal tissue lining the cavities of the inner ear. This path of extension strongly suggests some direct channel, such as that shown to exist and would explain the areas of change seen in the various parts of the labyrinth capsule. The whole process appears to be a slow form of inflammation, a definite series of reactions of a special tissue to repair damage caused by some unknown element, bacterial or toxic. As a result of their investigations the authors arrive at the following conclusions. (1) Some cases of otosclerosis (spongification of the labyrinth capsule) appear to be of the nature of a blood infection, and may be called "primary." We would expect that further research would show that in these cases the bony changes are widespread throughout the skeleton. (2) Other cases of otosclerosis undoubtedly follow attacks of catarrhal or purulent otitis media, the infective process invading the labyrinth capsule at the anterior margin of the oval window. Such cases may be called "secondary." (3) From the clinical stand-point, heredity plays an important part in otosclerosis, but, as the condition is a chronic inflammatory process, the infective agent must gain access to the labyrinth capsule either through the blood-stream or from the middle-ear cleft. (4) It has been proved by clinical and microscopic research that "atypical" cases of otosclerosis exist in which functional examination of the ear reveals the presence of nerve deafness. The relationship between the bony changes and the nervous affection is not yet clear.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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The Minimum Number of Bacilli Required to Transmit Tuberculosis to Guinea-pigs.—I. Thöni and A. C. Thaysen (*Zentralbl. f. Bakteriol.*, 1916, Part 1, p. 308) report the following: The dose of injection was standardized by Burri's method, which permits an accurate count of the bacteria. In the first series of experiments 19 guinea-pigs were injected with a highly pathogenic culture, the individual doses of which contained between 10 to 76 tubercle bacilli. Only one pig, the one which had been injected with 71 bacilli and which died after forty-one days with symptoms of dysentery, showed signs of tuberculosis. In a second series of experiments 3 strains of the bacillus, two of which were highly virulent, were employed. Twenty-two guinea-pigs received doses containing between 99 and 343 bacilli. No tuberculosis developed.

These results are at variance with the ones obtained heretofore. Previous experiments of others seemed to have shown that one or few (10 to 20) bacilli are sufficient to convey tuberculosis. The author believes that the previous experiments are erroneous. He believes that the methods employed to standardize the bacterial emulsion did not permit a high degree of accuracy.

The Comparative Resistance of Bacteria and Human Tissue Cells to Certain Common Antiseptics.—Lambert (*Jour. Exp. Med.*, December 1, 1916, xxiv, No. 6) found that the comparative resistance of bacteria and human tissue cells to antiseptics and other chemicals may be easily tested by tissue cultures under conditions which approximate those found in the living body. A comparative study shows that while human cells (connective tissue and wandering cells) are highly resistant to many antiseptics, they are in general more easily killed than bacteria (Staphylococcus aureus). Of the antiseptics tested, which include mercuric chloride, iodine, potassium mercuric iodide, phenol, tricresol, hydrogen peroxide, hypochlorites (Dakin's solution), argyrol, and alcohol, the one which approaches most closely the ideal disinfectant is iodine, which kills bacteria in strengths that do not seriously injure connective-tissue cells or wandering cells.

Anaphylactic Shock in Dogs.—J. P. Simonds (*Jour. Infect. Dis.*, December, 1916, xix, No. 6) concludes that anaphylactic shock in the dog is associated with a fall in blood-pressure. During the period of low pressure the reaction to injections of epinephrin is either absent or greatly diminished, while the response to nicotin may be augmented. It is believed that the mechanism of the latter is chiefly dependent on its effect on respiration, and only to a very limited extent or not at all on direct stimulation of the vasomotor center or the sympathetic ganglia. There is evidence for the belief that there is present a condition of decreased irritability of the sympathetic ganglia and possibly of the vasomotor center. The prompt rise in arterial pressure after injections of nicotin associated with dyspnea is evidence that in anaphylactic shock in the dog there is no constriction of the vessels of the lungs.

Destroying Lice on Typhus Fever Suspects.—S. R. Grubbs (*Public Health Reports*, October 20, 1916, xxxi, No. 42) states that in excluding typhus fever from the United States it is important to have some efficient and rapid method of killing lice on the human body. As a result of studies made at the Boston quarantine station, the United States Public Health Service has adopted a method of treating persons with a gasoline soap spray and shower bath and of treating clothing and baggage with a vacuum hydrocyanic acid gas process. The formula for the gasoline soap is as follows: Soap chips or laundry soap, 1 part; soft water, 4 parts; gasoline, 4 parts. The soap is dissolved by boiling in the water and the gasoline is added after removing from the fire. This mixture hardens to a jelly and for spraying, 1 part of this is mixed with 5 to 10 parts of hot water. Each person is sprayed thoroughly from head to foot with the gasoline soap solution and then compelled to walk through a shower tank 15 feet long, 10 feet of this under the shower which washes off the soap. For the treatment of lousy clothing

and baggage different methods have been tried but the treatment with cyanide seems to be the most advantageous. The method of cyaniding is that used to cyanide cotton bales to kill the pink ball worm, and consists of creating a vacuum in a metal chamber holding the articles to be disinfected, liberating cyanide gas in the chamber and allowing air to enter which forces the gas into the articles. Experiments performed to decide the length of time and the amount of vacuum necessary to thoroughly disinfect tight packages of various kinds showed that lice in ordinary hand-baggage will be killed by the vacuum-cyanide method with fifteen in vacuum and 30 minutes' exposure to hydrocyanic acid gas from four ounces of Na C.N. per 100 cubic feet. If trunks are to be treated by this method, the lids should be opened. After disinfection clothing and baggage are returned to the owner free from vermin; but otherwise in an unchanged condition. The method of generating the cyanide is simple and inexpensive, and the generator may be attached to any steam chamber while for the vacuum an electric or gasoline driven air-pump will work rapidly and successfully. Hydrocyanic gas has very slight power to kill bacteria and should not be used for this purpose.

Experiments on the Destruction of Body Lice.—Friedman (*Zentralbl. f. Bakteriol.*, 1916, Part 1, p. 320) carried on laboratory experiments with the view of reproducing actual conditions. The lice were packed into several layers of woollen, silk and other fabric and then exposed to various destructive agents. Live steam killed the parasite and the eggs within five minutes. In the municipal steam disinfection operators it required three hours' exposure to obtain a similar result (three larvæ developed subsequently in the exposed material). A ten-minute exposure to dry air of 70° C. is very efficient. Five commercial powders (trade name not given) were examined and found to be of no insecticidal value. Further experiment showed that lice will eagerly look for woollen fabric and that they will shun silk. They will deposit eggs on wool and none on silk if they have their choice. The development of larvæ on silk is very much delayed. An exposure of lice to carbon disulphide at 12° C. for twenty-four hours in a closed bottle proved very effective. The fumes penetrated five layers of wool and other material. The smallest quantity of carbon disulphide required for efficient work was 54 to 57 mg. per liter of air and a six-hour exposure. With sulphur dioxide 100 mg. of the gas per liter of air and four to five hours' exposure seemed necessary to kill the parasite. Sulphur dioxide is a very destructive gas and carbon disulphide is to be preferred.

Experiments on the Immunization against Louse Bites.—Galli-Valerio (*Zentralbl. f. Bakteriol.*, 1916, Part 1, p. 262) experimented on his own person, rubbing at various times 40 different substances on his forearm and placing P. cervicalis within, on the edge, near the medicated area. He permitted these lice to bite him, making observations on the frequency of bites. Not one of the substances, most of which were essential oils, proved to be of positive immunizing value.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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The Relation of the Bronchisepticin Skin Reaction to Immunity in Canine Distemper Including the Bactericidal Action of the Dog Serum for B. Bronchisepticus.—KOLMER, MATSUNAMI and HARKINS (*Jour. Immunol.*, 1916, i, 571) cite some very interesting experiments in which they endeavored to discover some relation between the bronchisepticin skin reaction and the immunity of dogs to distemper. In a previous article in the same journal, Kolmer, Harkins and Reichel described the preparation of bronchisepticin, their technic in using it as well as some results which were obtained in animals inoculated with this antigen. In the previous experiments the results indicated that there was little or no relation between immunity to distemper and the bronchisepticin skin reaction, though experimentally the reaction did have some diagnostic value. The experiments cited in the present communication are more complete and they confirm the previous conclusions. The present work included observations on the agglutination, bacteriolysis and complement-fixation tests on the sera of dogs having the disease at the time of the experiments, of dogs which had recovered from the disease and of dogs which had been vaccinated with an emulsion of dead bronchisepticus organisms. The tests were all carefully controlled and the readings of the results were very interesting but in all they tended only to prove that the relation of this skin reaction to immunity from Bacillus bronchisepticus is practically "nil." The authors emphasize, however, that even though this last be true the test has a diagnostic value in that a very high percentage of positive reactions is obtained in dogs having distemper and also in dogs which have recovered from this disease.

The Relation between the Thyroid and Parathyroid Glands.—In a recent study, TANBERG (*Jour. Exper. Med.*, 1916, xxiv, 547) has brought forward some evidence to show that the accepted views on the functional coöperation between the thyroid and parathyroid gland may require readjustment. In a previous paper, this writer had demonstrated that in rats an excessive meat diet produces hypertrophy of the thyroid appearing in the gross as an increase in size and weight, and microscopically as a proliferation of the epithelial elements, with at the same time a loss of the colloid substance. In the present work,

cats are used. The same results were obtained in these animals when kept on a diet consisting entirely of meat and water. However, it was noted that if insufficiency of the parathyroids was induced in meat-fed animals by the extirpation of two or more of these small glands, the usual hypertrophic picture did not develop in the thyroid. It was found, too, that the hypertrophy of the thyroid induced by a meat diet disappeared after excision of a sufficient number of parathyroids. In one instance, the animal lived, though a chronic tetany developed, after excision of four (microscopically demonstrated) parathyroids. In it, tetany was accompanied by a rapid decrease in size of the hypertrophic thyroid which had previously been developed in this animal by a meat diet. This unusual occurrence, in which an animal lived after excision of apparently all the parathyroid tissue was cleared up by the discovery of a fifth parathyroid when the animal was killed, more than a year after the first operation. Its thyroid was of normal appearance, though the animal had lived on a diet consisting solely of meat and water. Indeed, in chronic tetany, an atrophy rather than a hypertrophy of the gland is often developed, regardless of the diet. This evidence seems to point to some interrelation between the glands, at least to the extent that parathyroid insufficiency interferes with the function of the thyroid. Complete extirpation of the thyroid, however, produces little change in the gross and microscopic appearance of the parathyroids. Small tags of thyroid tissue which may be accidentally left during experimental thyroidectomy, take on a compact appearance, with small alveoli and scanty colloid; this hypertrophic picture may bear some resemblance to parathyroid tissue. In chronic tetany in which the remaining parathyroid tissue is insufficient, this tissue undergoes a curious hypertrophy, with the development of large transparent sharply defined cells having nuclei rich in chromatin. This picture differs from the hypertrophy of the parathyroids seen when the remaining glands are able, by this means, to compensate for parathyroid loss. In this latter condition, the remaining parathyroids assume a slight increase in size. The parenchymal cells definitely increase in size and uniformity of outline, though the increase does not approach that seen in chronic tetany. Animals with complete excision of the thyroid and the internal parathyroids, rapidly show symptoms of marked cachexia, but without evidence of tetany. These facts indicate that a decrease in parathyroid tissue may be compensated by that remaining, but that in the absence of the thyroid, none of its functions are undertaken by the parathyroids. Hence the author concludes that aside from the occurrence of direct or indirect interaction between the two glandular systems, the thyroid and parathyroids must be considered as independent organs each with specific functions, and that no proof of the existence of vicarious coöperation between the two has been established.

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ORIGINAL ARTICLES

SOME NEUROLOGICAL OBSERVATIONS IN 150 LAMINECTOMIES FOR SPINAL DISEASE AND INJURY.[1]

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(From the Surgical Services of the New York Neurological Institute and the Mount Sinai Hospital.)

During the past six years I have had the occasion to make a number of observations upon 150 patients with diseases or injuries of the spinal cord who were subjected to surgical interference. Some of the observations are here recorded, so that others may check up our results and report upon their own experiences.

Root Pains in Spinal Disease. Pearce Bailey and Joseph Collins have recently published papers in which they point out that frequently extramedullary spinal disease has, contrary to the general opinion, a painless beginning, while intramedullary disease may be characterized by the early appearance of root pains. Many of the cases reported by these authors were operated upon by the writer, and very often the operative findings gave the explanation for the presence or the absence of early root pains.

Thus we have found that in extramedullary tumors which develop under a slip of the dentate ligament, root pains are often missed among the early symptoms. The explanation for this is to be found in the anatomical relations between the dentate ligament and the posterior roots. The ligament lies in front of the posterior

[1] Read at the Meeting of the Section for Nervous and Mental Diseases, New York Academy of Medicine, October 10, 1916.

roots, and it is easy to understand that the latter are, to a considerable degree, protected against pressure from in front by the interposed dentate ligament.

We have made the interesting observation that large tumors are softer in consistency than the small ones, and are less apt to cause marked cord symptoms until the growth has attained a very large size. The small tumors, on the other hand, are often very hard, and rapidly exert considerable pressure upon the cord. Some of the large soft tumors do not cause pressure upon the nerve roots for a long time, and in cases of this kind, root pains as early symptoms are often wanting. In the large soft growths which surround the roots of the cauda equina (giant endotheliomas) early root pains are likewise relatively infrequent. It is surprising how little pain is complained of by a patient in whom the lower end of the spinal canal is filled with soft tumor growth which surrounds and envelops all of the nerves of the cauda equina.

I have operated upon several patients with small extramedullary growths on the posterior surface of the cord, who gave no history of pain as an early symptom of their disease. In these patients the tumor lay in the mid line of the cord on its posterior surface and had not attained a sufficient size to compress the origins of the posterior roots on either side. It is well known that excepting for the lines of attachment of the posterior roots, the spinal cord is not sensitive to pain, and the explanation for the painless early course in some patients with small extramedullary new growths is to be found in this insensitiveness of the cord tissue.

In intramedullary spinal tumors, on the other hand, early root pains do occur, and we have seen and operated upon two patients in whom the localized swelling of the cord from the growth occurred under a posterior root, so that the root was stretched very early and root pains were complained of among the earliest symptoms of the disease.

I do not wish to be understood as denying that early root pain is most frequent in extramedullary tumors and is relatively rare in intramedullary new growths, but the exceptions to this rule are so numerous, that one can not rely upon this symptom alone to differentiate between diseases which begin outside of or within the cord tissue.

The Sensory Symptoms in Spinal New Growths. In the majority of instances, a spinal disease which causes spastic paraplegia without any disturbance of sensation, is to be classed as a degenerative process in the motor pathways of the cord, but frequent exceptions to this rule occur. For example, I have operated upon a young woman and removed a large soft glioma which lay in the median line on the posterior surface of the cord in the upper dorsal region, in whom repeated careful examinations by experienced neurologists failed for many months, to find any sensory disturbance

at all. The history of this patient is of sufficient interest to report in detail:

Large extramedullary tumor of cervical cord; laminectomy and removal; cure.

Annie R., aged nineteen years, admitted to the surgical service of Dr. Sachs, at Mt. Sinai Hospital, on May 16, 1913. The patient had been seen for a number of months by Dr. Abrahamson, because of the complaint of a feeling of weakness in both lower limbs. Examination showed that the lower limbs were somewhat weak and that the knee and ankle-jerks were slightly exaggerated. There were no sensory disturbances of any kind. Three months before admission, the patient fell to the ground and when she was picked up, she found that her right leg was much weaker than her left leg. From this time on the weakness grew gradually more marked and the right leg became increasingly stiff. The left leg has also become somewhat stiff and weak. Since her fall, the patient has had urgency of urination with occasional loss of control of the vesical sphincter.

Physical Examination on Admission. The patient was a healthy looking young woman. Cranial nerves normal. Power in upper limbs good; reflexes not exaggerated; equal on both sides. Abdominal reflexes were present and equal. Power in lower limbs poor, but the right is much weaker than the left. Both limbs were very spastic. Knee-jerks exaggerated, right greater than left; ankle-jerks exaggerated, bilateral ankle clonus and Babinski. Wassermann and roentgen ray negative. Careful examination failed to reveal a disturbance of sensation in any part of the body.

May 18. A lumbar puncture was done and 6 c.c. of clear yellow fluid not under increased pressure were removed. After the spinal puncture, the patient began to complain of pain in the right shoulder.

May 20. Today, for the first time, there is some diminution in pain and temperature sensation up to the level of the second dorsal area, most marked on the left side. Tactile sensation is normal all over the body.

May 21. There is now complete loss of pain and temperature sensation up to the second dorsal level, but light touch is distinctly felt over the affected areas. Deep muscle sense is also not affected.

May 22. Today, for the first time, there is some diminution of tactile sensation below the area of distribution of the second dorsal segment, and more marked on the left side of the body. By evening of the same day, there was complete anesthesia over the affected areas, and the patient was transferred to the Surgical Service for immediate operation.

Laminectomy was performed on the same evening, by Dr. Elsberg, and a large soft tumor was exposed which lay on the posterior surface of the cord and was so closely connected with the cord that its removal was put off for a second operation. Two weeks

later, the wound was reopened, and the large soft, well encapsulated growth was easily removed. It was 6 cm. in length and at least 1 cm. in width. Pathological report was glioma. Convalescence was uneventful. Within two months most of the motor and sensory symptoms had disappeared, and one month later she was entirely well.

As I have already mentioned, in the large soft tumors which grow around the conus and the roots of the cauda equina, sensation in the lower extremities is either normal or the changes are so slight that the examiner is often in doubt as to the reality of the slight sensory changes. It is most surprising, after the examination has failed to reveal marked sensory disturbances in the lower limbs, to find at operation a large tumor which fills up the lower part of the spinal canal and has grown between and around the nerves of the cauda equina. The absence of sensory disturbances can only be explained on the basis of the soft consistency of the new growth.

Many benign extradural tumors cause for a long time, very vague and indefinite sensory changes. I have operated upon several patients in whom the diagnosis of spinal cord tumor was not made for a long time because of the slight and irregular sensory disturbances. The following patient was watched in the out-patient department of the New York Neurological Institute for many months by Dr. E. L. Zabriskie and by the writer. Distinct objective sensory changes were found long after motor cord symptoms had already been prominent.[2]

Extradural Fibroma of Cord; Laminectomy and Removal. Cure. A. K., aged eighteen years, first came to the out-patient department of the New York Neurological Institute in September, 1913. For three months his friends had told him that he walked with a staggering gait and he himself noticed that he was unsteady on his feet. Several times he was so unsteady that he fell to the ground. This was his only complaint. He was examined by Dr. Zabriskie, but aside from an unsteadiness when he walked, nothing abnormal could be discovered. The patient entered the hospital and repeated careful examinations were made. The reflexes were normal, power in the lower limbs good, no evidence of any sensory disturbance. In October the reflexes in the lower limbs became exaggerated and he developed ankle clonus and Babinski on the left side. At this time there were irregular and very indefinite areas of disturbed sensation on the anterior surfaces of both thighs. After a few weeks stay in the hospital, the patient was discharged and returned to the out-patient department at regular intervals. For a number of months, he was watched by Dr. Zabriskie but no definite areas of disturbed sensation could be made out. In December, 1913, his

[2] I am indebted to Dr. Collins and Dr. Zabriskie for permission to publish this case.

condition grew worse, walking became more difficult so that by the beginning of January, 1915 (seven months from onset of his illness) he was unable to walk or stand unless supported. About this time he began to complain of pain in the right side of the abdomen. He was readmitted to the institute on the service of Dr. Collins on February 11, 1914.

Physical examination now showed the following: The abdominal reflexes were present and equal. The cremasteries could not be obtained. Knee- and ankle-jerks exaggerated, left more than right; exhaustible ankle clonus on left side; Babinski and Chaddock on left. Complete loss of deep muscle sense in left lower extremity. The patient has lost all power in the lower limbs except for slight flexor power at the left knee. The sensory disturbances are very indefinite. There seems to be a slight diminution in tactile and pain sense up to the level of the twelfth dorsal segment. The sensory loss is more distinct over the outer surface of the left leg. It is difficult to say with certainty that there is any disturbance of temperature sense, but it is very slight at the best.

Laminectomy, February 14, 1914 (by Dr. Elsberg): Removal of spinous processes and laminæ or dorsal ninth, tenth, and eleventh. To the right of the tenth dorsal segment, outside of the dura was a bluish tumor mass over which a nerve root was tightly stretched. After division of the nerve root, the growth was easily removed. Convalescence uneventful. All of the symptoms rapidly improved. The patient was presented at the meeting of the New York Surgical Society in April (two months after the operation) subjectively well. One month later, physical examination failed to show any evidence of the previous motor and sensory disturbances. The tumor was reported a fibroma.

Remarks. This case presents a number of features of interest. The presence of motor symptoms long before the appearance of any evidence of sensory disturbance is unusual. When the sensory disturbances finally appeared, they were very indefinite and irregular. Root pain (pain in the right side of the abdomen) appeared only seven months from the beginning of his illness in spite of the fact (as demonstrated at the operation) that the eleventh dorsal root was stretched over the tumor. Finally, the fact of most marked motor disturbanee on the opposite side, is of great interest. We have observed this in several instances. It is to be explained by a kind of contrecoup. The spinal cord was pushed to the left by a tumor on its right side, so that the left side of the cord was pressed against the bony wall of the spinal canal resulting in more interference with the left than with the right pyramidal tracts.

Several years ago we had under observation a patient in whom the diagnosis of multiple sclerosis was finally made, in whom sensory disturbances were most marked on the anterior surface of the body.

Since that time, we have examined a number of patients who suffered from a variety of diseases (extradural and intradural tumors, disseminated sclerosis, syringomyelia, stab wound of the cord) in whom the sensory changes on the anterior surface of the body were more marked than on the posterior surface. In several patients, with slight but distinct hypesthesia and hypalgesia on the anterior surface of the trunk and lower limbs, the sensation on the posterior surface was normal. If the diminution of feeling over the front of the body was very marked, that on the back was often much less distinct. I have never, however, seen any difference between the anterior and posterior surfaces of the body when the sensation on the anterior has been entirely lost. While this observation may have been recorded by others, the only reference to the subject I have been able to find is one by Redlich (Neurologisches Centralblatt, 1915, No. 22) who noticed a difference between the sensory disturbances over the front and the back of the trunk in some cases of cerebral hemianesthesia. Recently I operated upon a patient who had a well marked Brown-Sequard syndrome from a stab wound of the back. There was distinct sensory loss affecting all three sensations up to the level of the sixth dorsal segment in front, while, on the back, the loss of sensation was so slight that there was some doubt whether the sensory loss was real or not. At the operation a knife blade two inches long was removed from the spinal canal. It had partially divided the lateral third of the cord.

In a number of patients, also, we have noted that, if pain and thermal sensation was diminished—the disturbance of thermal sense was more marked than that of pain sense. In many cases of spinal compression sensitiveness to pain was markedly diminished over definite areas, while the recognition of and the differentiation between hot and cold was lost entirely.

OBSOLETE MILIARY TUBERCLES OF THE SPLEEN.

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Tuberculosis of the spleen is most commonly observed in cases of widespread miliary tuberculosis. In the not uncommon miliary disease of children and early adolescence, the spleen is usually involved in an intense infection of its tissues. Under these conditions the localization of the infection is mainly through a filtration of the blood by the spleen. The spleen, however, becomes only one of the many tissues in which the microörganisms locate.

The tubercles which arise through the activity of this infection are all of about the same age, showing fairly uniform characters and common stages of development. At autopsy these lesions are seen in the acute or subacute stages, and are scattered in innumerable quantities through the spleen pulp.

The spleen also has been found to be the seat of primary tuberculosis. In the use of the term "primary" it is not meant that the spleen is the portal entry or even the first lesion induced by the invasion of the tubercle bacillus. The term is rather meant to suggest that the pathological process brought about in the spleen is more marked than found elsewhere, and not uncommonly the advanced tuberculous lesion of the spleen leads to a further dissemination into other parts. Thus not a few cases of the so-called primary tuberculosis of spleen show evidence of an older lesion in the thorax with, it may be, very recent tubercles in other tissues. The splenic lesion thus lies intermediate in time and has antedated some of the tuberculous processes of other organs. Not a few of the cases of primary tuberculosis of the spleen have been observed clinically and have received surgical intervention by splenectomy. In these cases it is obvious that although the splenic manifestations have been most prominent during life, no definite information can be offered as to the sequence of events in the tuberculous process. It is interesting that in these cases of primary tuberculosis of the spleen the organ is often found definately enlarged.

To this group of tuberculous infections of the spleen must be added the one here under discussion, the healed or partially healed miliary lesion. Little or no note has been made by students on tuberculosis upon the healing of multiple miliary nodules within the spleen. The early stages of the development of the miliary tubercle is well known and has been much studied. These stages have been accurately followed through the proliferative reactions and the process of caseation. The growth of fibroblasts in the periphery of the advanced nodules has also been discussed, but few have reported observations upon the subsequent fate of the tubercle.

In our earliest observations upon the shot-like, mustard-seed nodules in the spleen we were unconvinced of their tuberculous nature. The fully headed nodule with its concentric layers of fibrous tissue and sharp demarcation from the surrounding spleen pulp, suggested a thrombotic origin of the fibrosis not unlike the formation of phleboliths in the pampiniform plexus of the testis. A further study, however, has given us an opportunity of seeing these nodules in the various stages of fibrosis. The lesions can be followed from the late caseous miliary tubercle with its surrounding fibroblasts to the definite encircling of the area with firm strands of connective tissue. Furthermore in some of the foci with advancing fibrosis evidence of the tuberculous process could be observed on the periphery in immediate contact with the sclerosing ring.

Autopsy No.	Sex.	Age.	Tuberculosis in organs.	Weight of spleen.	Fibrosis in spleen.	Nodules in spleen.	Previous history.
6	M.	42	Obsolete peribronchial glands and spleen	900	Fibrosis	One small calcareous	History of tuberculosis in family. Died of cirrhosis of liver.
16	M.	26	Obsolete spleen and liver	664	Adhesions	Numerous small hard and yellow nodules	No history of tuberculosis. Died of lobar pneumonia.
38	M.	42	Obsolete spleen.	95	Fibrosis.	Many small hard nodules, and one 0.75 cm.	No history of tuberculosis. Died of heart, kidney and arterial diseases.
40	M.	42	Obsolete peribronchial glands and spleen	260	None	Occasional small calcareous nodules	No history of tuberculosis. Died of pyemia.
51	M.	37	Obsolete tracheal glands, spleen and liver	240	Adhesions	Occasional small calcareous nodules and one in accessory spleen	History of tuberculosis not given. Died of chronic empyemia.
98	M.	61	Obsolete peribronchial, mesenteric glands, spleen and liver. Obsolescent of lungs and peribronchial glands	165	Fibrosis	Several small hard yellow nodules	No history of tuberculosis. Died of pernicious anemia.
103	M.	64	Obsolete spleen	160	Fibrosis	One small hard yellow nodule	Died of heart, kidney and arterial diseases.
105	M.	63	Obsolete lung, peribronchial glands, spleen and liver	75	None	Many small hard nodules	No history of tuberculosis. Died of apoplexy (arteriosclerosis.
107	M.	23	Obsolete lung, peribronchial glands, spleen and liver	70	None	Several small hard nodules	Died after severe accident.
122	M.	53	Obsolete peribronchial glands and spleen	140	None	Two small hard nodules	No history of tuberculosis. Died of gonorrheal polyarthritis.
134	M.	43	Obsolete lungs, peribronchial glands & spleen. Obsoleseent lungs & retroperitoneal glands	215	None	Many small calcified nodules	Pneumonia two years previously. Died of acute lobar pneumonia.
146	M.	42	Obsolete liver, spleen and mesenteric glands	350	None	Two small calcified nodules	Died of cancer of duodenum.
152	M.	36	Obsolescent lung; obsolete liver and spleen	750	Adhesions	Many hard calcareous nodules	Died following railroad accident.
169	M.	48	Caseous tuberculosis of lungs with cavitation. Obsolete spleen and liver	90	None	One hard shot-like nodule	Died of chronic pulmonary tuberculosis.
173	M.	69	Obsolete lungs, peribronchial glands, liver and spleen	95	None	Occasional small calcareous nodules	Died of fracture of skull.
180	M.	43	Obsolete spleen	150	Adhesions	Two small hard yellow nodules	No history of tuberculosis. Died of acute toxic jaundice.
201	M.	26	Obsolete spleen	?	Adhesions	Many small calcified nodules	Died of diphtheria.
223	M.	20	Obsolete liver and spleen	130	None	Many small seed-like bodies	Died of acute nephritis.
242	M.	21	Obsolete spleen	225	None	Two firm nodules with pin-point areas of necrotic tissue in center	No history of tuberculosis. Died of bronchiectasis and abscess of lung.
298	M.	49	Obsolete spleen	85	None	Single firm yellow nodule	No history of tuberculosis. Died of acute lobar pneumonia.
300	M.	28	Obsolete spleen	190	None	Single hard nodule with necrotic center	No history of tuberculosis. Died of acute lobar pneumonia.
308	F.	39	Obsolete peribronchial glands and spleen	195	None	Many small hard nodules	No history of tuberculosis. Died of operative hematoma.
315	F.	70	Obsolete lung and spleen	75	Fibrosis	Some small shot-like nodules	History of chronic bronchitis. Died of bronchopneumonia.
333	F.	50	Obsolete spleen	140	Adhesions	Several small calcareous nodules	Died of acute lobar pneumonia.
349	M.	52	Obsolete spleen	200	Fibrosis	One small firm nodule	No history of tuberculosis. Died of syphilitic cirrhosis of liver.

Autopsy No.	Sex.	Age.	Tuberculosis in organs.	Weight of spleen.	Fibrosis in spleen.	Nodules in spleen	Previous history.
350	M.	30	Tuberculous bronchopneumonia. Obsolete and obsolescent peribronchial glands. Acute miliary lungs, spleen and liver. Obsolete spleen	300	None	Many small hard yellow nodules and many gray miliary tubercles	No previous history of tuberculosis. Died of acute miliary tuberculosis. Illness ten days simulating typhoid.
353	M.	25	Obsolete spleen	175	Adhesions	Many firm nodules with calcification	Died of Hodgkin's disease.
359	F.	18	Obsolete peribronchial glands spleen and lung. Obsolescent peribronchial glands	130	None	Several hard fibroid nodules size of mustard seeds	No history of tuberculosis. Died of acute gastro-enterocolitis.
360	F.	54	Obsolete peribronchial glands and spleen	115	None	One fibrosed nodule	No history of tuberculosis. Died of chronic cholecystitis.
413	M.	36	Caseous tuberculosis of lung with cavitation. Obsolescent peribronchial glands and intestine. Obsolete liver and spleen	225	None	Several hard calcified nodules, the size of mustard seeds	Died of chronic tuberculosis and pyopneumothorax.
422	M.	28	Obsolescent peribronchial glands and lung. Obsolete lung and spleen	90	None	Several small hard nodules, size of mustard seeds	Died of acute lobar pneumonia.
478	F.	36	Obsolescent peribronchial glands Obsolete liver and spleen	195	Adhesions	Numerous round yellow white nodules	Died of rupture of uterus.
480	M.	35	Acute tuberculous peritonitis. Obsolescent peribronchial, retroperitoneal and omental glands, prostate and lung. Obsolete lung, spleen, liver and adrenal	?	None	Several hard round nodules	Died of tuberculous peritonitis.
516	M.	40	Obsolescent lung. Obsolete spleen and liver	250	None	Several small yellowish nodules	Died of acute lobar pneumonia.
522	M.	63	Obsolete peribronchial and mediastinal glands, and spleen. Acute miliary lung, kidney & spleen. Tuberculous ulcer of larynx	85	None	One small hard calcified nodule	Died of miliary tuberculosis.
534	M.	49	Obsolete spleen	125	None	Many fibrous and calcified nodules size of mustard seeds	Died of acute alcoholism and pneumonia.
511	F.	47	Caseous tuberculosis of lung with cavitation. Obsolete lung, peribronchial and mesenteric glands & spleen	125	None	A single firm white nodule	History of tuberculosis in family. Died of chronic tuberculosis.
567	M.	45	Obsolete spleen	360	None	Few small hard nodules	No history of tuberculosis. Died of appendicitis and peritonitis.
582	F.	42	Obsolescent peribronchial glands and adrenals. Obsolete peribronchial glands liver and spleen	?	None	Several small hard yellow nodules	Died of Addison's disease.
P-2898	F.	55	Obsolete spleen	175	Fibrosis	Several hard yellow nodules	History of cholelithiasis, jaundice, operation; death from hemorrhage.

To the naked eye the obsolete lesion is characteristic. The shot-like yellow nodules stand in strong contrast to the spleen pulp. The sharp demarcation without an infiltrating fibrosis differentiates the lesion from other sclerosing processes. However, it is impossible by the naked eye to state whether such discrete nodules are fully healed or are only in the obsolescent stage. We have found that nodules, hard and shotty, may still contain within them small remains of caseous material or even evidence on the outer border of a reaction suggesting a still active process. It is, of course, possible that the nodules with peripheral reaction have become the site of a new infection.

The material forming the basis of this report was obtained from 404 autopsies on individuals over ten years of age. In this series of autopsies particular attention was given to noting the presence of tuberculous foci in all parts of the body. Out of the entire series, tuberculosis was noted in 172 cases. The spleen was involved in a tuberculosis process in 69 cases. Of these there were 40 instances in which healed or almost completely healed tuberculous lesions, subsequently to be described, were found.

Of the 40 cases there were 31 males and 9 females. The average age was forty-two, the youngest being eighteen and the oldest seventy. In all but 12 cases old tuberculous lesions were found elsewhere, most frequently in the peribronchial lymph glands or in the lung. In the majority of instances the individual did not suffer from active tuberculosis and clinically no evidence of such infection was observed. Three patients, however, showed a persistent or chronic tuberculosis of the lungs; another died of tuberculous peritonitis, while 2 others died of an acute miliary tuberculosis. Other than these 6 cases the tuberculous lesion or lesions which were present elsewhere than the spleen were in the obsolete or obsolescent stage. In 28 cases an old tuberculous lesion outside of the spleen was found, and in the 6 cases suffering from active tuberculosis this antedated the recent dissemination. An interesting finding was the presence of healed miliary tubercles in the liver. Of these there were 15 cases, in 2 of which the liver and spleen were the only organs involved. These healed tubercles of the liver closely resembled those found in the spleen. They were small, round, and shot-like, without evidences of active tuberculosis in the organ.

Other than the characteristic tuberculous nodules in the spleen, this organ varied very much in its appearance. In weight it ranged from 76 to 900 grams. The average weight was 219 grams while there were twenty-four below 200 grams. As the finding of the old tuberculous lesions in the spleen was in the majority of cases only incident and as the individuals had died of various infections and accidents, the characters found within the spleen cannot entirely be referable to the old tuberculous lesions. It would appear from our

table that the presence of this tuberculous process has no marked influence upon the weight of the organ. The presence of fibrous adhesions about the spleen or of an increase of the fibrous tissue within the spleen, was noted in 15 cases. Such fibrosis or adhesions may have been associated with the acute stage of the tuberculous infection; however, all of these changes cannot be referred to the tuberculous process alone, as cirrhosis of the liver and chronic infections probably played a part in changing the structural character of this tissue. There were many instances in which no characteristic change was to be noted in the splenic structure other than the isolated fibrous nodules of old tuberculosis. In 2 cases the old and discrete tuberculous processes of the spleen were associated with more recent miliary tubercles in the active and progressive stages. This would indicate a second dissemination of tubercle bacilli reaching the spleen.

The miliary tubercle of the spleen in the healed or almost healed state differs quite markedly in its appearance from similar lesions in other organs save the liver. It appeared in the character of a small nodule of hard consistence and usually spherical. The type most commonly met with appeared like a small yellow concretion about the size, shape, and color of a mustard seed. Occasionally larger nodules were found, of somewhat irregular shape and measuring up to about 0.75 cm. in diameter. These nodules were irregularly scattered through the spleen substance, and their yellow color was in sharp contrast to the dark red pulp of the organ. They were found directly beneath the capsule or sprinkled through the parenchyma of the spleen. Their outer border was sharply demarcated from the spleen tissue, and they are quite easily removed from the surrounding structure. In their periphery there was no evidence of fibrosis extending into the surrounding parts. At times in shelling out the nodules the outer capsule was found to remain in the spleen tissue forming a small cup-like cavity. The discrete character of the nodules and the absence of change in their immediate vicinity was always striking.

The number of these nodules varied from a few to a large number. Occasionally small clusters were found, but in the majority of instances the discrete masses were irregularly scattered at some distance from each other. The macroscopic appearance of the tissues forming the nodules have been fairly uniform. They were hard and shot-like, and the outer coats consisted of concentric layers of fibrous tissue which could be removed in successive laminæ. The centers of the nodules were either hard and calcareous or fibrosed, some of them still showing soft necrotic material. The necrotic substance when present formed very small, almost pin-point areas in the immediate center. In a few instances a relationship between the nodules and the vascular channels was observed.

The finding of 12 cases in which tuberculous foci were alone

found in the spleen is remarkable. At first sight one would be tempted to suggest that the finding was dependent upon a careless search for other lesions. In a number of cases, however, a distinct note was made at the time of autopsy that this was the only focus discovered. In these cases the splenic lesions differed in no way from those found in the remaining series.

There is one common characteristic possessed by all of the nodules which we have examined. This consists of the mature concentric layers of connective tissue which surround them and sharply demarcate the nodule from the spleen pulp. The spleen tissue immediately

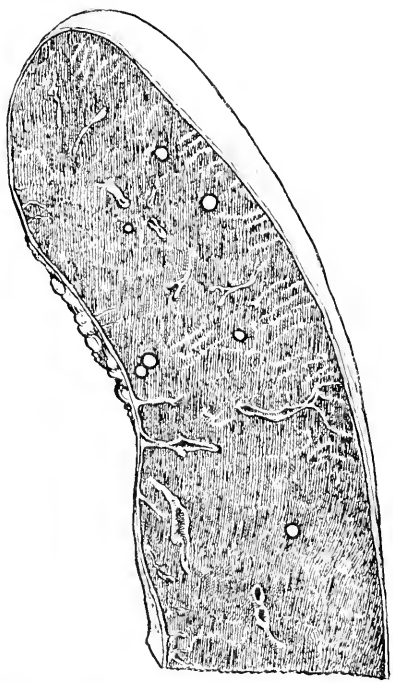

FIG. 1.—Spleen with obsolete miliary nodules of tuberculosis.

beyond the outer border of the nodule commonly showed no evidence of reaction, nor was its architecture changed. The fibrous tissue in the nodule did not send any trabeculæ into the surrounding tissue. This sharp line of demarcation in the absence of any response in the spleen pulp was quite remarkable. In some of the more recent lesions, those that had not advanced to complete healing showed more or less lymphocytic infiltration in the tissues immediately surrounding the nodules, and in 4 instances this was accompanied by the presence of small and recent tubercles in the progressive and active stages. In some cases it appeared that these

tubercles were associated with and dependent for their existence upon the main tubercles which had not reached the final stage of healing. In 2 instances recent tubercles were found in the spleen

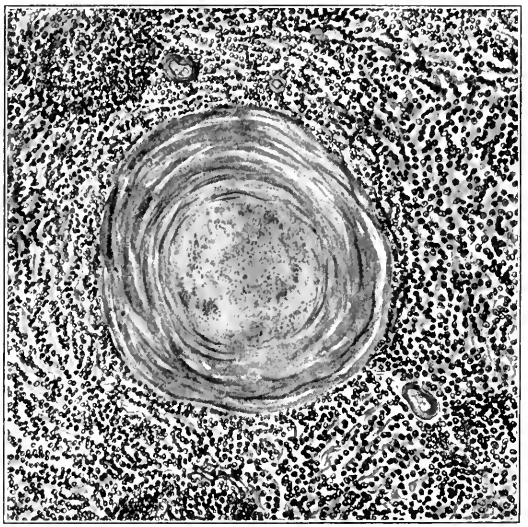

FIG. 2.—Fibrosed nodule with remnants of central necrosis.

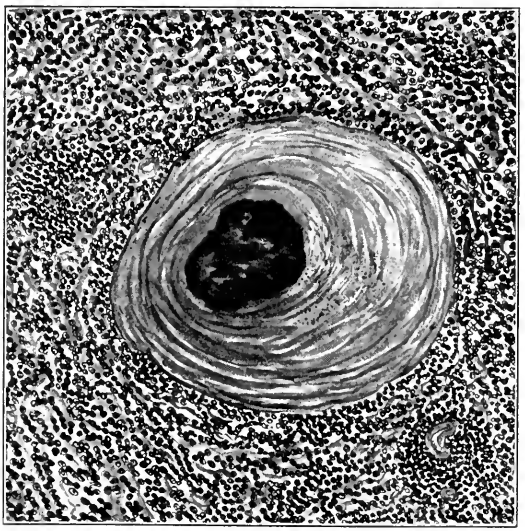

FIG. 3.—Fibrosed nodule with central calcification.

quite unassociated with the old nodules, but indicating a new hematogenous miliary distribution, as was indicated in the generalized miliary tuberculosis found elsewhere.

The size of the obsolete tuberculous lesions of the spleen indicated that during the active stage they consisted not of a single tubercle but of several closely approximated lesions. It is probable that, like the development of the ordinary miliary tubercle, the process began in a single tubercle, but with the development of necrosis and the multiplication of the tubercle bacilli a number of new tubercles were developed in the periphery. Thus numerous tubercles developed upon the circumference of the enlarging area until a size was attained which was readily distinguished by the naked eye.

The disposition of these old foci in the spleen was irregular and at times difficult to define. In some of them the remains of the central artery of the Malpighian body could still be seen within the fibrosed tubercle. These arteries were still patent and the fibrous tissue immediately bounding them was disposed in a direction concentric with the vessel. At other times it appeared as if the tubercle had developed within the pulp substance at a distance from the Malpighian body and unassociated with the trabeculæ of the spleen.

Although the nodules have, on naked-eye examination, a very similar appearance, and though they all have the common characteristic of being surrounded by a dense laminated connective tissue the central area may differ quite widely. In some the concentric layers of connective tissue continued throughout the nodule; others contained a small mass of granular necrotic material; the remains of former caseation in the center. The latter showed no evidence of an active process insofar as a tissue reaction was concerned. The necrotic material was firmly bounded by a wide border of dense connective tissue without evidence of lymphocytes, endothelial cells, or giant cells. A varying amount of calcification was also seen in these areas of necrosis. At times this consisted of a fine granular precipitate while in others a definite concretion formed a central nucleus.

The manner of laying down of the connective tissue is interesting. In the early development of the miliary tubercle in the spleen the proliferative response giving rise to the new cells of the tubercle leads to the crowding aside of the essential tissues of the area. The fine reticular stroma with its lymphocytes and endothelial cells is pushed outward, so that in the immediate periphery of the tubercle they appear to lie in a concentric fashion. At this early stage there is no increase in this reticular tissue. Soon, however, this neighboring stroma without actual proliferation increases the thickness of its strands by the accumulation of hyalin or collagen. It has thus been not uncommon to find a peripheral border of a heavy collagen containing connective tissue forming a lacework surrounding the tubercle, from which the lymphocytes gradually disappeared. When the lymphocytes accumulate it is usually to the outer side of this stroma. This connective-tissue boundary continues to exist with the increasing growth of the tubercle, but not until a reparative

process appears about the active foci does the original connective-tissue capsule increase to any definite degree. The laying down of new connective-tissue bands takes place on the inner side of this connective-tissue layer. Fibroblasts make their appearance in the small tubercles bounding the caseous center and gradually the characteristic architecture of the tubercle becomes disturbed until the giant cell lying within the jumble of fibroblasts and a few endothelial cells is all that remains of the active granuloma As the fibroblasts gradually lay down the permanent collagen fibers they are disposed in a concentric fashion. The disappearance of the fibroblast itself is rapid until nothing remains save the dense laminated collagen fibers. It was very apparent in these nodules that after the disappearance of the active process the new growth of connective tissue advanced but slowly. The caseous material in the center gave no evidence of tissue stimulation, and its absorption and removal was a slow procedure. Thus advancing fibrosis toward the center was a matter of time during which the central débris was being slowly removed.

Many sections of the fibroid masses, as well as of nodules with small caseous centers, were searched for tubercle bacilli but none were found. I would place no individual stress upon the negative finding obtained in material which had been stored in preservatives for more than a year, but as we have had similar results in dealing with tissues of more recent origin, I am inclined to view these structures as devoid of infection. At what stage in the healing process the microörganisms are destroyed cannot be stated, but it is probable that the event bears comparison with similar lesions in the lymph glands, as has been described by Warthin.

In 2 cases of recurrent infection of the spleen we have demonstrated tubercle bacilli in the progressive tissue lesions lying outside of the hard nodules, while no bacteria were found in the healed lesion. As we have previously stated these peripheral tubercles may have been a hematogenous reinfection of the spleen, or it may be that the bacteria had escaped from the primary miliary foci during the earlier stages of their development. In the latter case, if true, the infection remained latent over a considerable period, so that the difference in the tissue reaction between the primary and secondary lesion was very apparent.

Discussion. The evidence that we have here presented of healed or healing miliary tuberculosis of the spleen has an interest both from the clinical and pathological view-point.

In the majority of the cases the distribution of the tubercle bacillus to the spleen had taken place from small foci having no clinical significance. The findings indicate that the peribronchial glands were most frequently the areas from which microörganisms were disseminated by way of the blood stream. It is probable that, at the time of the bacillary distribution, several organs became

the point of localization, and we have evidence that in 15 cases the liver was simultaneously involved with the spleen. In the majority of instances, however, miliary lesions of contemporary infection were lacking elsewhere. It is obvious that scattered miliary lesions induced in many tissues escape our eye after the process of healing is complete and when the local damage is of small extent. We cannot claim that in our series of autopsies all cases of healed miliary lesions of the spleen were observed, as isolated nodules may readily escape detection. It is, however, striking that as many as 40 cases should have come to our notice in a series of 404 autopsies on individuals over ten.

The absence of clinical data of any symptoms, whereby the time of infection of the splenic tissues can be indicated, gives us no opportunity of determining the age and rapidity of the healing process of localized miliary tuberculosis of the spleen. The early fibrosis developing about tuberculous areas after a period of six weeks or several months has been well studied in man and animals. Such reactionary fibroses, however, are still in the proliferative stage when fibroblasts and young connective-tissue cells are laying down an outer wall about the area of necrosis. The majority of lesions in our cases, however, were much more advanced and were devoid of evidence of active proliferation except in the instances where more recent recurrent infection had localized in the vicinity of the old lesion. The concentric bands of connective tissue were in the mature state, and in some instances in a process of hyaline transformation. Months of time would bring little alteration in their structure. It is well seen that such encapsulation would permit only of slow organization of remnants of the caseous process. In some instances calcification of the central area supervened but in others a fine and granular necrotic material still remained. Whether any infection was still present in the central areas of necrosis could not be finally determined. We were unable to demonstrate tubercle bacilli in this material, but whether latent infection was still available must remain unanswered until inoculation experiments are undertaken. As the material with which we were dealing had been preserved from autopsies performed at different times in the past five years, we were unable to carry out all of the studies necessary to clear up many of these points.

A point worthy of comment is that the presence of these old tuberculous foci had no marked effect upon the uninvolved portion of the spleen. In a number of cases adhesions were found; in a few others there was fibrosis. By no means, however, was the fibrosis marked and often when noted it was more relative than real. Furthermore, in some cases the fibrosis had a direct relation to an intercurrent disease process. Likewise there was no constant evidence of splenic enlargement resulting from the presence of old tuberculosis. It has been indicated that in the so-called primary

tuberculosis of the spleen one of the not unusual manifestations is the increase in weight and volume of the organ. The reported cases of primary tuberculosis of the spleen were observed in the acute or obsolescent stage. In these instances the focus of infection was of fair size, often occupying a considerable portion of the organ. Under these conditions the spleen showed definite enlargement. It is not uncommon that in acute miliary tuberculosis in which the spleen among other organs becomes the site of innumerable tubercles, its weight is materially increased. It may well be that during the acute process of infection of the cases reported in our series, the spleen was more or less enlarged. The condition, however, was transient leaving no characteristic organic change in its internal structure.

The distribution of the tuberculous infection was hematogenous. Whether the primary portal of entry was through the respiratory or alimentary system is immaterial. Undoubtedly, however, the infection primarily found localization in some other tissues where, after multiplication of the microörganisms and destructive changes in the involved structure, the bacteria found entrance into the blood stream. That no fatal outcome resulted at the time of this blood-stream dissemination indicated that relatively few bacteria were discharged from the initial focus. We have interesting evidence, therefore, that the quantity of infection of miliary tuberculosis varies greatly, and that the outcome of such distribution depends upon the relation between the amount of infection and the resistance of the tissues in which the bacteria locate. In these cases of old tuberculous foci in the spleen we have observed encapsulated nodules varying in number from one to very many.

A considerable interest has recently been taken in the role of the lymphocyte in tuberculosis. Bartel believed that he was able to demonstrate, by experiment, that a direct antagonism existed between lymphatic tissues and the tubercle bacillus. Primarily, it was found that a hyperplasia of the lymphoid structures along with an endothelial proliferation took place. These lymphatic tissues not only act as filters for the microörganism, but also offer a protective mechanism for the body. In many instances the infection of animal tissues by the tubercle bacillus is unassociated with structural change, even though the microörganisms are present in the tissues. Bartel has been able to demonstrate the tubercle bacillus within lymph glands in which no other change than hyperplasia had occurred. These bacteria he found were much reduced in virulence. Lewis and Margot found that there was a relation between the function of the spleen and the resistance of an animal to tuberculosis. Commonly after the inoculation with tubercle bacilli the spleen became enlarged. In mice it was found that splenectomy prolonged the life of the inoculated animals. No explanation could be offered for these apparently divergent results.

Ths importance of the spleen in counteracting infection, not only within its own tissue but also of a systemic kind, was shown in the experiments of Hektoen and of Simonds and Jones. These authors brought about partial destruction of the spleen by the application of the roentgen ray. After intense or prolonged exposure the animals developed a greater susceptibility for infection. This susceptibility appeared to be the result of a decrease in the lysins of the blood as well as a decided inhibition in the production and activity of the leukocytes. However, as the use of the roentgen-ray on small animals is not limited in its influence upon the spleen alone, it is possible that the change in the quantity of immune bodies is also dependent upon the effect of the rays upon the other hemopoietic organs. Somewhat more confusing results have been obtained by the use of benzol. This substance has a marked influence in depressing the production of leukocytes by the bone marrow, at the same time it was shown by White that prolonged treatment of rabbits by benzol led to the development of a much enlarged spleen. This occurred even when the leukocytes of the blood had been reduced more than one-half. Under these conditions of an enlarged spleen and diminished leukocytes the animal showed an increased susceptibility to the tubercle bacillus as compared to the untreated animals.

There appears, therefore, to be good evidence that the spleen has a definite relation to the development of immune bodies in various animals. This function is probably a limited one, and is similar to that possessed by other hemopoietic tissues. Whether the resistance of the spleen to infection differs greatly with the various microörganisms is not clear, but it would seem that, like other lymphatic tissues, its antagonism to the tubercle bacillus is quite marked.

Of the 40 cases of healed miliary tubercles of the spleen, 15 showed similar lesions in the liver. The liver nodules were identical with those in the spleen, being round and hard and of the size of mustard seeds. They were distributed irregularly through the liver substance, and usually were few in number. More frequently they were found in the periphery of the lobule, in direct contact with the fibrous tissue of the portal systems. Their sharp demarcation from the surrounding liver tissue was as striking as in the spleen, and the absence of associated tissue change in other parts of the liver was constant. Whether the microörganisms located in the liver at the time of the general hematogenous distribution, or whether the liver infection was gained by the portal blood from the spleen cannot be stated. Both routes of infection are available, and a portal distribution during the active process in the spleen might readily occur.

In view of the high incidence of liver infection in all cases of tuberculosis, as is claimed by some, it is remarkable that healed miliary

nodules do not appear more frequently. If, as Ullom states, tuberculosis of the liver develops in from 70 to 100 per cent. of the cases, the mode of distribution must in large part be hematogenous, and Rolleston believed mainly by the portal vein. In our own observations we have failed to find tuberculosis of the liver as frequently as stated, though we have never undertaken a systematic search by the microscope. As is observed by all, the tuberculous lesions of the liver are most often of insignificant size and discovered only by microscopic search. The lesions which we have observed associated with the spleen nodules were all recognized by the naked eye at the autopsy table. Their character was so uniformly similar to those in the spleen as to suggest a synchronous deposition. Moreover, they would also indicate a tissue resistance to this infection equal to that of the spleen, suggesting a systemic as well as a local organic origin for the immunity. In no instance where healed miliary tubercles were found in the spleen had the liver infection progressed to conglomerate tubercles or cavitation. Even in those cases of pulmonary tuberculosis in which the tissue progressed to caseation and cavitation of the lungs the foci in the liver and spleen remained small and were well advanced in healing. These differences in the healing process of various tissues offer interesting studies in tissue immunity.

We find but little reference in the literature to the presence of healed miliary lesions in the spleen. Abbott in the *Catalogue of the McGill Medical Museum* mentions one specimen presented by Adami of the character as we have described. In an analysis of 1000 autopsies Adami and McCrae found evidence of healed tuberculosis in 151 cases and of these, healed lesions were present in the spleen twice while obsolescent lesions were seen four times. Winternitz has given a very full review of the work on tuberculosis of the spleen, in which he makes particular reference to the so-called primary tuberculosis, a condition quite different from that which we have under discussion. The lesions described by him usually refer to large caseous masses which have led to much enlargement of the spleen to be recognized clinically. A considerable number of these cases were treated surgically by splenectomy. Although the spleen is spoken of as the seat of acute or subacute miliary infection no reference is made to the healed lesion. The frequency of splenic involvement in tuberculosis is given by Reinhold, who found tuberculosis of the spleen in 67 per cent. out of 428 cases of tuberculosis in children, and in 19 per cent. out of 836 cases in adults. In our own series of 404 autopsies tuberculosis was present 172 times and the spleen was involved in 69 cases. In 40 of the latter healed miliary lesions were found in the spleen, 2 of them showing a reinfection with a fresh crop of tubercles. Sternberg in a discussion upon peculiar types of tuberculosis with characters of pseudoleukemia noted the tendency to fibrous encapsulation of tuberculous processes in the spleen. Colet and Gallavardin referred

to the finding of partly sclerosed nodules in the spleen of a man, aged sixty years. The liver in this case also had nodules which were still caseous. The report on focal tuberculosis of the spleen by Fischer deals with subacute lesions in which caseation occupies the center of the nodule while the periphery is made up of proliferating epithelioid and giant cells. None of the lesions observed by him had reached the obsolete stage. Brohl excised the spleen of a patient aged forty-eight years, and found six small yellow concretions which contained calcium carbonate and phosphate, and which he believed had their origin in phleboliths.

More comparable to the described lesions of the spleen are those reported by Warthin occurring in the mesenteric glands. Warthin claimed to find evidence of healed tuberculosis in the mesenteric glands with great frequency. The tissue changes consisted in part of hyaline deposits as well as small fibrosed nodules with central débris and a peripheral laminated structure. The latter lesions appeared very similar to those which we have observed in the spleen. On no occasion, however, have we found the centers to consist of a hyaline substanec. The hyaline transformation of the neighboring stroma was frequently observed in the spleen in the presence of tuberculous foci. Warthin found similar hyaline and sclerosed masses in the bronchial glands of adults.

A word must be said about the 12 cases of healed miliary tuberculosis of the spleen in which no other focus was found in the body. As we have previously indicated, search was made at the time of autopsy for other tuberculous manifestations, and none were found. We cannot but doubt that some unrecognized focus had existed near the point of entrance of the infection, but that recognizable tissue change was no longer evident. The splenic infection had undoubtedly developed through blood infection in which other organs had also received localized foci. It would appear that the tuberculous process had been dealt with unequally in the various tissues, all save the spleen clearing themselves of the invading organism before permanent damage was done. In the spleen, temporary tissue destruction was brought about with subsequent complete healing. In these cases it would appear that the resistance of the spleen to tuberculous involvement was not so great as in other tissues. These findings would indicate that a tuberculous bacteriemia may occur in the absence of an advanced localized focus of infection and that a miliary distribution may be overcome by the individual tissue resistance.

Conclusions. In a series of 404 autopsies, tuberculosis was met with in 172 cases. The spleen was involved 69 times, and in 40 of these miliary lesions were completely or almost completely healed by fibrosis.

The average age was forty-two years and the youngest was eighteen years. Six of the cases showed a persistent tuberculosis in other organs. In 15 cases the liver also contained healed miliary tubercles.

In none of the cases had there been recognizable clinical manifestations of splenic involvement. The spleen was not enlarged. In 12 cases with healed miliary tubercles of the spleen no other tuberculous process was found.

The splenic infection was a hematogenous one arising most commonly from antecedent foci in the lungs or peribronchial glands. Those cases in which no primary tuberculous focus was found probably had a similar mode of origin in which, however, the initial focus was of minor extent unrecognizable at the time of autopsy. We would point out that the fibroses which are observed in anthracotic peribronchial glands are difficult of analysis as indicating a preceding infectious origin of the fibrosis.

The healed splenic tubercles are recognized only by careful search and complete gross sectioning of the tissues of the organ. The presence of the healed miliary tubercles of the spleen indicates the frequency of a tuberculous bacteriemia from which the tissues may entirely recover. The different organs demonstrate a variable resistance to the tuberculous infection. Reinfection may take place in the spleen.

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THE ASSOCIATION OF GASTRIC SYMPTOMS IN NEPHRITIS WITH RETENTION OF NITROGENOUS WASTE PRODUCTS IN THE BLOOD.[1]

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Since the time of Richard Bright it has been recognized that renal disorders are accompanied by digestive disturbances. The

[1] Read before the American Gastro-enterological Association, Washington, D. C.

pathological basis for this association has been the source of much speculation for the reason that there are no physiological facts which adequately explain it. The symptoms occur in all stages of the disease, from the most incipient to the furthest advanced. Many cases of unrecognized nephritis have only symptoms of dyspepsia. We have been particularly impressed with the number of cases of latent nephritis sent to the hospital with a diagnosis of gastric ulcer or of toxic vomiting. The more common symptoms from which patients of this type complain are nausea, vomiting, loss of appetite, flatulency, abdominal distress, usually without definite relationship to meals, and headaches, frequently of the migrainous type. Owing to the depressed gastric secretion the diagnosis of asthenic gastritis is occasionally made. On account of the toxic character of the vomiting these patients are frequently told that they are suffering from enterogenous intoxication.

In view of the important advances recently made in the estimation of the various nitrogenous waste products which accumulate in the blood (and tissues) in nephritis it appeared of interest to compare the type and extent of this retention with any gastric symptoms which might occur. The end-products of nitrogenous metabolism which deserve consideration are the uric acid, urea, and creatinin. As has already been pointed out in contributions from this institution,[2] uric acid is normally the most difficult and creatinin the easiest to eliminate. It is not surprising, then, that very early cases of nephritis should show a retention of uric acid without any corresponding retention of urea or creatinin, while cases in the last stages of the disease should be the only ones in which a decided increase in creatinin is encountered. Following this scheme we have divided the cases we propose to discuss into two groups, viz., those showing high creatinins and others in which the high uric acid was the prominent feature. This arrangement has been made for the reason that the retention of creatinin has been found to be of great prognostic value in nephritis[3] while the uric acid appears to be an early diagnostic sign. The cases showing marked nitrogen retention, particularly with respect to the creatinin, will first be considered. The similarity in the gastric symptoms in this group of 10 fatal cases (see Table I) is very striking. It is worthy of note that 3 of these cases (II—T. D., VI—E. P., and VII —J. W.) were called to my attention on account of their gastric symptoms. Although examination at once revealed the fact that these patients were suffering from nephritis, the gravity of the situation was not appreciated until a blood examination disclosed a marked retention of creatinin. These cases greatly impressed me and, in a measure, suggested the title of the present paper. Their histories are worthy of brief review:

[2] Myers, Fine, and Lough: Arch. Int. Med., 1916, xvii, 570.
[3] Myers and Lough: Arch. Int. Med., 1915, xxi, 536.

Case II.—T. D., male, aged thirty-four years, at the time of admission to the hospital, on January 13, 1915, was able to be up and about. His chief complaint was vomiting and pain in the epigastrium of five to six months' duration. A chemical blood examination was made and gave a creatinin of 7.8 mg. to 100 c.c., showing that the patient was in the terminal stages of interstitial nephritis. He died on March 23, 1915.

Case VI.—E. P., female, aged forty years, was admitted to the hospital with a history of persistent vomiting for the previous two months. Physical examination showed a fairly well-nourished woman with no evidence of edema. The chemical examination of the blood not only established the diagnosis of nephritis, but the high creatinin (8 mg. to 100 c.c. of blood) gave a fatal prognosis. The woman died six weeks after leaving the hospital.

Case VII.—J. W., male, aged thirty-four years, walked to the hospital and was admitted on February 22, 1915, complaining of headaches, nausea, vomiting, and constipation. A blood examination gave a creatinin of 8.3 mg. Clinically the patient quickly improved and was continuously up and about the ward. He repeatedly requested to be allowed to go home, but as the creatinin of the blood remained high, he was persuaded to remain. He was up on April 14, but on becoming faint was put to bed, gradually declined, and died on April 16, 1915.

Figures for the CO_2-combining power of the blood (according to Van Slyke's method) are given for 5 of the 10 cases. Although these are all low it is scarcely believed that the acidosis bore a causal relation to the vomiting. Although we have no definite evidence showing that the nitrogenous waste products have such a relationship it is of some significance that the gastric symptoms seem to vary, to a certain extent, with the amount of retention.

In Table II are tabulated 12 cases with gastric disturbances in which the special feature of the blood analysis is the high uric acid. Many of these cases showed symptoms directly comparable with the preceding group, although none of them was terminal. In general the symptoms were more mild than the preceding, but it seems safe to conclude that they were the early manifestations of the same general condition.

In cases of migraine the estimation of the uric acid of the blood has been of great value in detecting a latent nephritis. Four years ago we were impressed with a case of this character.

D. L., aged forty-five years, had suffered from periodic attacks of typical migraine for the previous five years. These attacks were intense and had resisted all forms of treatment both here and abroad. Examination of his blood proved to be normal with the exception of a uric acid retention of 5 mg. per 100 c.c. When treatment was instituted to reduce the uric acid accumulation in the blood the sick headaches suddenly stopped and have not returned. The only

TABLE I.—GASTRIC SYMPTOMS AND BLOOD FINDINGS IN FATAL CASES OF NEPHRITIS.

Case.	Age.	Sex.	Urine.		Blood-pressure.		Phthalein 2 hrs. Per cent.	CO_2 combining power. C.c. to 100	Blood-sugar. Per cent.	Uric acid.	Urea nitrogen.	Creatinine.	Gastric symptoms.	Result.
			Albumin.	Casts.	Systolic.	Diastolic.				Mg. to 100 c.c. of blood.				
I—S. H.	37	M	++	++	220	138	0	..	0.14	14.3	262	22.2	Vomiting; gaseous eructations	Died.
II—T. D.	34	M	+++	+	210	105	0	..	0.14	14.3	152	20.5	Nausea; vomiting; epigastric pain	Died.
III—I. D.	17	F	++	++	182	138	0	..	0.19	27.0	209	20.0	Vomiting; abdominal pain	Died.
IV—P. J.	43	M	+++	−	..	..	0	31	0.25	12.5	162	20.0	Vomiting 2 mos.; duration	Died.
V—E. C.	50	F	++	−	210	100	..	..	0.09	22.4	236	16.7	Vomiting 2 yrs.; constipation; poor appetite	Died.
VI—E. P.	40	F	+++	+	205	145	0	39	0.19	4.2	46	12.5	Vomiting 4 mos.; epigastric pain; constipation	Died.
VII—J. W.	34	M	++	++	220	100	trace	..	0.14	8.7	144	11.0	Nausea and vomiting; constipation	Died.
VIII—O. G.	22	M	++	−	225	115	23	45	0.13	7.3	65	4.5	Vomiting 2 weeks	Died.
IX—P. L.	47	F	+	−	127	85	13	27	0.16	13.3	28	4.3	Vomiting; no relation to food intake; constipation	Died.
X—M. S.	62	M	++	+++	195	100	18	20	0.08	7.3	30	4.0	Vomiting.	Died.

Normal blood findings: CO_2 combining power 54 c.c. per 100, sugar 0.10 per cent., and uric acid 2–3, urea N 12–15, and creatinine 1–2.5 mg. to 100 c.c.

TABLE II.—GASTRIC SYMPTOMS AND BLOOD FINDINGS IN NON-FATAL CASES OF NEPHRITIS.

Case.	Age.	Sex.	Urine.		Blood-pressure.		Phthalein 2 hrs. Per cent.	Blood-sugar. Per cent.	Uric acid.	Urea nitrogen.	Creatinine.	Gastric symptoms.	Result.
			Albumin.	Casts.	Systolic.	Diastolic.			Mg. to 100 c.c. of blood.				
I—M. S.	41	F	+	++	140	75	53	0.09	6.7	22	1.5	Vomiting; abdominal pain; diarrhea	Improved.
II—A. R.	57	M	−	−	130	70	40	0.12	6.3	22	2.5	Gaseous eructations; no vomiting; constipation	Unimproved.
III—J. C.	69	M	+++	−	150	100	20	0.11	6.3	40	1.5	Vomiting; diarrhea	Unimproved.
IV—P. P.	28	M	+	+	135	70	61	0.11	6.3	15	2.4	Vomiting; regurgitation of food; appetite poor	Improved.
V—M. S.	46	F	+	+	210	150	51	0.12	6.1	12	2.6	Vomiting; flatulency; constipation	Unimproved.
VI—L. B.	50	M	−	−	160	95	40	0.11	5.4	11	0.9	Vomiting; no relation to food intake	Improved.
VII—N. B.	71	M	+	+	130	75	54	0.11	5.4	17	2.8	Occasional vomiting	Improved.
VIII—A. B.	38	F	−	+	110	80	50	..	5.0	27	3.3	Vomiting; gaseous eructations	Improved.
IX—G. G.	61	M	+	+	210	110	48	0.11	4.8	22	3.4	Nausea and vomiting; constipation	Improved.
X—L. K.	72	M	+++	++	200	100	..	0.12	4.6	37	1.8	Epigastric pain	Improved.
XI—F. S.	67	M	+	+	125	90	16	..	4.2	10	1.5	Occasional vomiting	Improved.
XII—S. F.	58	F	+	+	190	70	44	0.12	3.7	22	3.2	Nausea and vomiting; epigastric pain	Improved.

other evidence of nephritis during the past four years has been an occasional faint trace of albumin in the urine with a systolic blood-pressure of 155 and a diastolic of 95. These conditions have been transitory.

Aside from the stomatitis and ulcerative colitis of uremia the gastro-enteric symptoms of nephritis are probably central. Evidence is lacking that uric acid, urea, and creatinin are toxic in themselves. The amount of their retention is a probable index, however, of the accumulation of unknown substances which may possess some toxic importance. A poor oxidation of creatinin in the absence of its excretion would give methyl guanidin, a substance of known toxic properties. The possible relation of such substances to the gastric symptoms of nephritis is, at present, only problematical.

NOTES ON CASES IN TABLE I.

CASE I.—S. H., male, aged thirty-seven years. Headaches; dizziness; constipation; alcoholic; had stomach trouble five months; vomiting; edema of feet and ankles. Diagnosis: chronic interstitial nephritis; died.

CASE II.—T. D., male, aged thirty-four years. Vomiting; epigastric pain for five to six months; alcoholic; constipation; had scarlet fever; weight in abdomen after food intake. Diagnosis: chronic interstitial nephritis; died.

CASE III.—I. D., female, aged seventeen years. Frontal headaches; epigastric pain; dizziness; vomiting; dyspnea; tachycardia. Diagnosis: chronic interstitial nephritis; died.

CASE IV.—P. J., male, aged forty-three years. Gastritis; diarrhea; headaches; dizziness; vomiting two months; edema of feet and ankles. Diagnosis: chronic interstitial nephritis; died.

CASE V.—E. C., female, aged fifty years. Dizziness; inability to pass urine; vomiting for past two years; no relation to food intake; constipation; nycturia. Diagnosis: chronic interstitial nephritis; died.

CASE VI.—E. P., female, aged forty years. Vomiting four months with headaches; slight epigastric pain; vomiting; bears no relation to food intake; constipation. Diagnosis: chronic interstitial nephritis; died.

CASE VII.—J. P., male, aged thirty-four years. Syphilis sixteen years ago; marked alcoholic; dyspnea; headaches; vomiting; edema of face and lower extremities fifteen months. Diagnosis: chronic interstitial nephritis; died.

CASE VIII.—O. G., male, aged twenty-two years. Fainting spells; impairment of vision; vomiting two weeks; alcoholic. Diagnosis: chronic interstitial nephritis; died.

CASE IX.—P. L., female, aged forty-seven years. Cough for three years; headaches; dizziness; palpitation of heart; constipa-

tion; vomiting; no relation to food intake; arthritis of right elbow. Diagnosis: carcinoma of liver; died.

CASE X.—M. S., male, aged sixty-two years. Headaches; occasional vomiting spells; dyspnea; increased frequency of urination; edema of feet and ankles; arthritis for ten years (?); enlargement of heart to right. Diagnosis: chronic interstitial nephritis, endocarditis; died.

NOTES ON CASES IN TABLE II.

CASE I.—M. S., female, aged forty-one years. Scarlet fever; diphtheria as child; abdominal pain; frequency of urination; diarrhea; vomiting; dyspnea. Diagnosis: neurasthenia; improved.

CASE II.—A. R., male, aged fifty-seven years. Constipation; gaseous eructations; nycturia; painful urination; no vomiting. Diagnosis: carcinoma of stomach and liver; unimproved.

CASE III.—J. C., male, aged sixty-nine years. Vomiting; diarrhea; edema of feet and ankles. Diagnosis: chronic interstitial nephritis; endocarditis; transferred; unimproved.

CASE IV.—P. P., male, aged twenty-eight years. Regurgitation of food; moderate alcoholic; occasional vomiting spell. Diagnosis: gastric ulcer (?); improved.

CASE V.—M. S., female, aged forty-six years. Weakness; anemia; headache; vertigo; cardiac pain; diarrhea; flatulence; epigastric pain; vomiting. Diagnosis: chronic interstitial nephritis; unimproved.

CASE IV.—P. P., male, aged twenty-eight years. Regurgitation of food; moderate alcoholic; occasional vomiting spell. Diagnosis: gastric ulcer (?); improved.

CASE V.—M. S., female, aged forty-six years. Weakness; anemia; headache; vertigo; cardiac pain; diarrhea; flatulence; epigastric pain; vomiting. Diagnosis: chronic interstitial nephritis; unimproved.

CASE VI.—L. B., male, aged fifty years. Headache; pneumonia eight years ago; vomiting spells every ten to fourteen days; no relation to food intake. Diagnosis: chronic interstitial nephritis; cecal stasis; improved.

CASE VII.—N. B., male, aged seventy-one years. Scarlet fever; constipation; pain in chest; difficulty in voiding. Diagnosis: chronic interstitial nephritis; improved.

CASE VIII.—A. B., female, aged thirty-eight years. Headache; stomach trouble seven months' duration; gaseous eructations; dyspnea; vomiting; accentuated P^2. Diagnosis: mucous colitis; improved.

CASE IX.—G. G., male, aged sixty-one years. Constipation; dizziness; vomiting three years; dyspnea; accentuated A^2. Diagnosis: chronic interstitial nephritis; hemiplegia; improved.

Case X.—L. K., male, aged seventy-two years. Pneumonia; diphtheria; epigastric pain; relieved after food intake. Accentuated A^2. Diagnosis: chronic pancreatitis; improved.

Case XI.—F. S., male, aged sixty-one years. Dyspnea; occasional vomiting spell; regardless of food intake; headache; weakness. Diagnosis: chronic interstitial nephritis; improved.

Case XII.—S. F., female, aged fifty-eight years. Arthritis in all joints (?); headache; dizziness; constipation; pains in shoulder; epigastric pain; nausea and vomiting; jaundice. Diagnosis: chronic interstitial nephritis; improved.

Conclusions. Gastric symptoms are among the most common early symptoms of nephritis. In cases with obscure gastric disturbances the chemical examination of the blood has been found very valuable. Several cases are reported in which the estimation of the blood creatinin not only showed that the patients were suffering from severe nephritis, but gave a fatal prognosis. In some of the earlier cases the blood uric acid was of value as an early diagnostic sign.

STUDIES IN THE PHYSIOLOGY AND PATHOLOGY OF THE STOMACH AFTER GASTRO-ENTEROSTOMY.[1]

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The operative treatment of ulcer of the stomach or duodenum is in the largest percentage of cases a curative one. Experiences, however, have demonstrated that the continuous repetition of instances demonstrating the splendid results obtained by operative interference is constantly and not infrequently being disturbed by a group of cases in which some of the preoperative symptoms persist after the surgical interference or in which new symptoms of an apparently different nature supervene during or after the period of recovery.

[1] Read by invitation at the Nineteenth Annual Meeting of the American Gastro-enterological Association, held at Washington, D. C.

Our efforts have been bent to studying the physiology and pathology of the stomach after operative procedures, and we have attempted by a careful analysis of the data, which we have thus far collected, to define and separate these cases into groups. We base the classification upon the clinical symptoms, the chemical findings, and upon a study of the gastric motor mechanism in the hunger state by means of kymographic tracings. For this last we have made use of the physiological methods employed by Cannon and Carlson, and have controlled the observations by radiographic examinations made by Dr. L. Jaches and his associates in the department of roentgenology.

This study comprises an analysis of 37 cases[2] of ulcer of the stomach and duodenum in which a posterior retrocolic gastrojejunostomy had been made. In all of these cases the ulcer-bearing area had been excluded by the string method or by pyloric plication, or had been removed by local excision, pylorectomy, or partial gastrectomy. These latter are relatively few in number.

Clinical Notes. The clinical symptoms following operation are of various kinds but fall naturally and readily into three classes:

Group A. The cases that do well after operation and have few or trivial symptoms. It has been found necessary to supervise carefully the postoperative diet of these patients in particular in regard to the curtailment of the amount of the alimentation. Under such a régime these patients are restored to health. There are 11 of these cases in the series.

Group B. This group includes those cases, 14 in number, in which, following operation, we were able to demonstrate a definite disturbance in the physiology of the stomach as exemplified in the secretory and motor functions. Clinically, the patients complain of definite dull, pressing, or cramp-like pain felt in the epigastric, substernal, or hypochondriac regions, and very often lower down in the perumbilical region or in the iliac fossæ. These pains are not identical with those felt before operation. They differ from the preoperative heartburn or from the colicky pain of pylorospasm. They are less severe, less definitely localized, and longer in duration. They often last throughout the whole or greater part of the digestive period. Vomiting is frequent; often it is repeated more than once daily after the taking of food; less frequently it occurs only once a day and then usually in the morning. The vomitus is not copious, and consists of sour biliary material. Food is frequently avoided because of the pain which it brings on.

[2] A few of the cases were originally operated upon while on the services of Dr. A. G. Gerster, Dr. A. V. Moschcowitz, Dr. C. A. Elsberg, and Dr. E. Beer. Some of the studies also were carried out while the patients were on the medical services of Dr. A. Meyer, Dr. N. E. Brill, Dr. E. Libman, and Dr. M. Manges. Our thanks are due to all of these gentlemen for their courtesy in permitting us to carry out these studies on their wards. We wish also to thank Dr. E. A. Aronson for the courtesy of permitting us to make some of these studies in the department of gastro-enterology of the dispensary.

The patient's weight may show some increase in spite of the gastric symptoms, but frequently an early increase is soon replaced by a loss.

The bowels are usually constipated, but occasional attacks of diarrhea may intervene.

Some degree of mental depression is frequently a pronounced symptom.

There are practically no physical signs; a moderate amount of diffuse epigastric tenderness is usual.

Group C. The third group is composed of cases in which mechanical disturbances in the function of the gastrojejunal stoma are present. There were 7 of these cases; 2 were instances of gastrojejunal ulcer and the remaining 5 of a gradually produced organic constriction of the stoma. The symptoms complained of were very similar to those in group B. The differentiation between groups B and C consists in the fact that in the former group there are functional disturbances and in the latter organic mechanical faults.

TABLE I.—CHEMISM OF THE STOMACH AFTER GASTRO-ENTEROSTOMY.

	Before operation.			1 to 4 months after operation.			4 to 12 months after operation.			1 to 4 years after operation.		
	Amt. c.c.	Free acid. %	Total acid. %	Amt. c.c.	Free acid. %	Total acid. %	Amt. c.c.	Free acid. %	Total acid. %	Amt. c.c.	Free acid. %	Total acid. %
Fasting stomach contents	45	..	..	33	9	28	33	9	19	20	15	27
Ewald test breakfast .	74	47	72	127	27	61	148	27	54	190	32	60
Riegel test meal . .	..	..	..	59	14	34	26	29	52	73	30	48

Chemism of the Stomach after Operation for Ulcer. In discussing this phase of the subject we shall follow the same group classification as heretofore described. Considering first the 37 cases as a whole by reference to the chart (Table I) it will be noted that before operation the average fasting morning residue in the stomach is 45 c.c.; the average Ewald test meal residue (one hour after administration) is 74 c.c., with free acid 47 per cent. and total acid 72 per cent. During the first four months after operation it is to be noted that while the fasting residue has not increased (in fact it has diminished) the average amount of Ewald test meal removed is 127 c.c., free acid 27 per cent., total acid 61 per cent. We observe that the operation has actually delayed instead of hastened the motility of the organ. The acidity, however, is diminished though not to a considerable degree. In the period from four to twelve months after the surgical interference the same observation is made, namely, that the fasting content remains low while the Ewald test meal residue has now increased to 148 c.c., the individual acidities remaining as before. In the cases studied one to four years after operation a still greater delay in motility is

seen, the Ewald residue having increased now to 190 c.c., the acidities remaining the same.

In corroboration of this fact we have the figures for the residual amount removed six hours after the administration of a Riegel motor test meal. Before operation no residue; one to four months after, 59 c.c. can be removed, free acid 14 per cent., total acid 34 per cent.; four to twelve months after, 26 c.c., with moderately low acidities. One to four years after the amount removed after the Riegel meal has increased to 73 c.c., a distinctly abnormal amount, considering that the normal stomach should have completely emptied itself in the prescribed period. In considering these figures we must be forcibly impressed by the fact that gastrojejunostomy is after all not a drainage operation, that contrary to general opinion the emptying power of the stomach is not accelerated but is actually and truly retarded, due to factors to be considered later. This fact is further emphasized by a consideration of the chemism of the stomach in each of these three groups previously described (Table II). Group A, comprising cases apparently well and free of symptoms, shows, nevertheless, that the residue, removed one hour after the usual Ewald meal, is 113.8 c.c. (before operation 74 c.c.), to be regarded as an abnormally increased amount, since our standard for an Ewald meal in a well person is usually regarded as below 100 c.c. The acidity is slightly diminished. When we consider groups B and C, patients with abnormal symptoms after the surgical interference, we note that the returns from the Ewald meal in the second group, those with functional disturbances, is 156 c.c., while in group C those with organic stenosis of the stoma, it actually reaches 237 c.c., the acidities remaining about the same in all three groups. The Riegel motor meal shows an increase, though only a moderate one.

TABLE II.—POSTOPERATIVE CHEMISM ACCORDING TO GROUP DIVISIONS.

	Cases well.			Cases with functional disturbance.			Cases with anatomical disturbance.		
	Amt. c.c.	Free acid. %	Total acid. %	Amt. c.c.	Free acid. %	Total acid. %	Amt. c.c.	Free acid. %	Total acid. %
Fasting stomach contents	26	11	20	23	15	29	38	15	32
Ewald test breakfast	113.8	31	59	156	32	62	233	32	57
Riegel test meal	23	19	28	60	35	65	40	19	53

The results of the individual examination may be seen by reference to Tables III, IV and V. That the disturbance is one not only of motility but also of the secretory activity in the proportion of solid residue to the supernatant fluid in the test meals. While the usual normal proportion of solid to fluid is about 1 to 1, after operation the proportion rapidly becomes 1 to 4 even in the supposedly well cases, while in those with recurrent symptoms it averages 1 to 2, though in individual instances it may reach 1 to 5 or even 1 to 7.

TABLE III, GROUP A.—CASES WELL AFTER OPERATION.

Case No.	Roentgen ray.			Chemism.									Kymographic tracing.
				Fasting stomach contents.			Ewald test breakfast.			Riegel test meal.			
	Stoma.	Pylorus.	Peristalsis.	Residue. c.c.	Free acid. %	Total acid. %	Residue. c.c.	Free acid. %	Total acid. %	Residue. c.c.	Free acid. %	Total acid. %	Tonus contractions.
4	Patent and efficient	Closed 6 months postoperative	....	30	0	18	225	24 (S:F::1:3)[3]	54	..	..	..	Good.
10	Patent and efficient	Patent and efficient	Slow	30	4	10	70	50 (S:F::1:2)	86	No residue			Poor.
16	....	....	....	5	0	0	20	0	56	No residue			Fair.
17	....	....	....	75	22	40	150	50 (S:F::1:8)	71	70	58	83	Fair.
19	Patent and efficient	....	Good (no residue)	10	0	0	60	0	14				
22	....	....	....	25	10	22	75	16 (S:F::1:4)	46	..	..	..	Good.
28	....	....	....	30	18	32	60	62 (S:F::1:2)	86				
30	....	....	....	25	44	56	210	38 (S:F::1:20)	54				
33	....	....	....	5	0	0	40	74 (S:F::1:7)	86	..	..	..	Good.
38	....	....	....	..	..	..	28	8 (S:F::1:1)	50				
6	Patent and efficient	Patent and efficient	....	70	0	10	80	0	12	..	..	..	Good.
		Total averages		26	11	20	113.8	31 (S:F::1:4)	60	23	19	28	

TABLE IV, GROUP B.—PHYSIOLOGICAL DISTURBANCES AFTER OPERATION.

Case No.	Roentgen ray.			Chemism.									Kymographic tracing.
				Fasting stomach contents.			Ewald test breakfast.			Riegel test meal.			
	Stoma.	Pylorus.	Peristalsis.	Residue. c.c.	Free acid. %	Total acid. %	Residue. c.c.	Free acid. %	Total acid. %	Residue. c.c.	Free acid. %	Total acid. %	
1	Patent; not efficient	Open after 6 months	Active; residue[4]	..	..	..	170	0 (S:F::1:2)	20	..	..	..	Fair.
2	Closed; not efficient	Open after 5 months	Residue[4]	25	10	22	220	38 (S:F::1:3)	63	..	..	..	Fair.
5	No evidence	Open after 10 months	Hyperperistalsis	90	46	48	300	44	64				
12	Very patent	Open after 5 months	....	16	10	25	160	11 (S:F::4:1)	45				
11	Inefficient	Open after 2 months	Active; residue[4]	65	21	41	125	36 (S:F::2:3)	68	..	..	..	Fair; poor.
15	....	....	....	50	0	15	150	30 (S:F::1:3)	50				
21	Inefficient	Open	Very active; sl. residue[4]	15	0	24	20	28 (S:F::1:1)	60	..	..	..	Poor.
25	Efficient	Open (no exclusion)	Hyperactive; no residue	25	18	31	70	32	94	35	36	62	Fair.
27	Efficient	Open after 4 months	Very active; no residue	18	40	54	50	52 (S:F::2:3)	92	50	46	86	
32	....	..	....	25	12	30	60	16	65	40	14	30	Fair.
35	....	....	....	..	..	..	150	74	95	70	80	94	Fair.
39	....	....	....	..	..	..	200	17	48				
9	Inefficient	Open	Residue[4]	1	0	0	350	14	51	100	0	55	
		Total averages		23	15.7	27	156	30 (S:F::1:2)	62.6	60	35	65	

[3] This refers to the proportion of solid to fluid ingredients in the test meal.
[4] = after six hours.

TABLE V. GROUP C.—ANATOMICAL DISTURBANCES AFTER OPERATION.

Case No.	Roentgen ray			Chemism.									Kymographic tracing.
				Fasting stomach contents.			Ewald test breakfast.			Riegel test meal.			
	Stoma.	Pylorus.	Peristalsis.	Residue. c.c.	Free acid. cc/c	Total acid. cc/c	Residue. c.c.	Free acid. cc/c	Total acid. cc/c	Residue. c.c.	Free acid. cc/c	Total acid. cc/c	
3	....	....	....	60	12	46	90 (S:F::1:2)	24	66	27	0	73	
13	No evidence	Open after 2 months	Violent residue[5]	44	8	21	190	30	64				
14	Inefficient; no evidence	Open after 1 year	Violent residue[5]	60	27	54	450 (S:F::2:1)	30	50	..	..	..	Good.
18	Patent inefficient	Open	Hyperperistalsis; residue[5]	50	27	41	210	34	52	..	..	..	Fair.
24	Inefficient	Open	Excessive activity	10	0	0	200	39	53	..	..	..	Poor.
26	....	....	....	5	..	..	600 (S:F::1:1)	33	50	30	0	18	Good.
27	....	....	....	..	..	..	230 (S:F::1:5)	33	64	70	30	50	Fair.
34	....	....	....	..	..	..	20	17	35	50	46	86	
		Total averages		38	15	32	105	42	77	20	22	36	
							233 (S:F::1:2)	32	57	40	19	53	

This is to be interpreted as an increase, often very marked, in the outpouring of gastric secretion, a hypersecretion associated with the

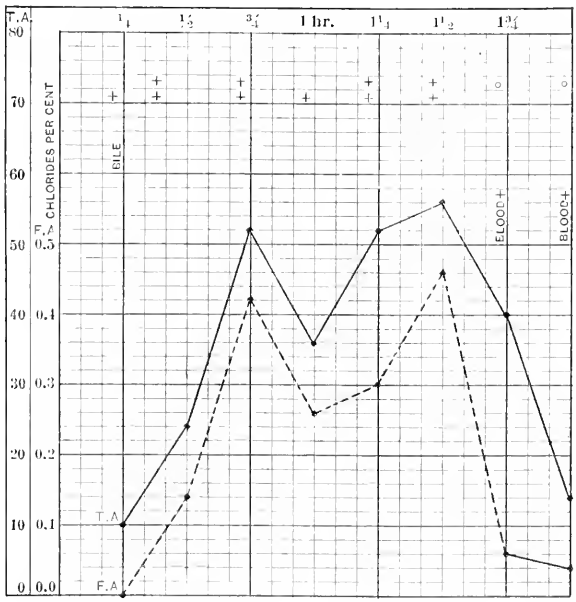

FIG. 1.—Gastro-enterostomy with string exclusion. Cured case.

delayed motility. The quantity of liquid residue removed often exceeds the amount of fluid actually administered in the test meal.

[6] = after six hours.

Our efforts further to elucidate the problem of gastric secretion after radical interference led us to adopt the method of fractional estimation of stomach contents as demonstrated by Rehfuss. Thin oatmeal water was utilized as the test substance and estimations made of the acidity of the stomach every fifteen minutes. This non-solid test substance is much more simple than the Ewald or Riegel foods, and gives slightly lower figures for the strength of acid secreted. With this test the cases in group A show a prac-

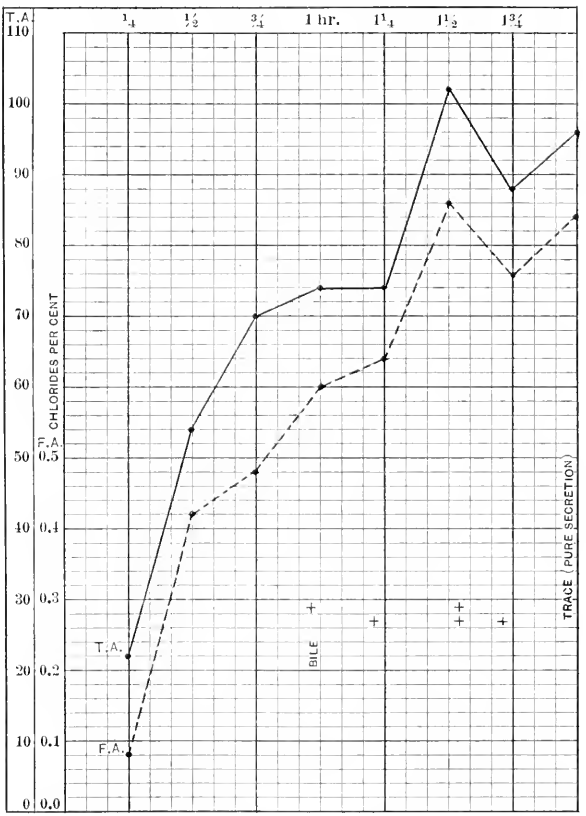

FIG. 2.—Gastro-enterostomy with exclusion by pyloric plication. Case with functional disturbances.

tically normal curve (Fig. 1), the acidity mounts gradually to the third period (three-quarter hour), then drops abruptly, due to the inflow of regurgitant intestinal contents, as evidenced by the admixture of bile; it then has a secondary rise lasting to the sixth or seventh period (one and one-half to one and three-quarter hours), following which the acidity diminishes as the end of the period of digestion approaches. The groups B (Fig. 2) and C (Fig. 3) follow the same course for the first five or six periods, but exhibit later a more prolonged and sustained secondary rise, lasting occasionally

to an eleventh or twelfth period (two and three-quarter to three hours) before the stomach is completely emptied. In these latter groups the acidity most frequently remains high to the end of digestion, never approaching the base line. In group B those cases with inefficiency of the stomach from functional causes the regurgitation of bile begins earlier and is greater in amount; the group of organic stenoses showed diminished intestinal regurgitation.

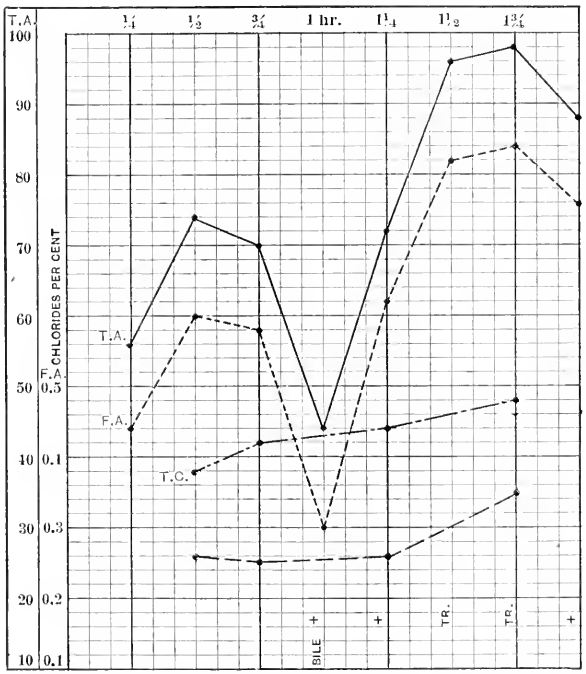

FIG. 3.—Gastro-enterostomy with string exclusion. Case with anatomical disturbances.

THE MECHANICS OF THE GASTRIC MUSCULATURE AFTER OPERATION. We have spoken often in this paper of the retardation of gastric motility. It is our contention that the delay in the emptying power of the stomach is due less to diminished peristaltic activity of the organ and more to diminution in the tone of the stomach wall (peristolic tone) and improperly coördinated muscular contractions. That an atonic and dilated stomach can still show vigorous contractions is generally conceded by all radiographers. That such is the condition after gastrojejunostomy we are able to demonstrate by two means: (1) by kymographic tracings of the empty stomach, and (2) by radiographic studies with the aid of the usual contrast meal.

The technic adopted by us for kymographic tracings is essentially that employed by Cannon and Washburn and Carlson and his collaborators in their well-recognized physiological studies of the

motor mechanics of the stomach wall of men and dogs. In the fasting state the patient is requested to swallow a small rubber balloon to which is attached a narrow-bore rubber tubing about thirty-six inches long. The efferent end of this tubing is attached by a T-shaped connection to both a mercury manometer and to a needle (by means of a tambour), which records on a slowly revolving drum the variations in intragastric pressures. Tracings are taken for one-half to three-quarters of an hour. The results obtained by this method of study of the peristolic tone of the stomach in the fasting state are most interesting and instructive. The normal stomach (Fig. 4) gives evidence of slow tonal contractions in its fasting state; these contractions follow each other quite regularly, the wave itself enduring for thirty to forty seconds, with a period of quiescence between contractions of usually thirty seconds. These are not peristaltic waves but are variations in the constant peristolic tonal state of the resting organ. A second type of contraction, the so-called hunger contraction (Fig. 5), is demonstrable in addition

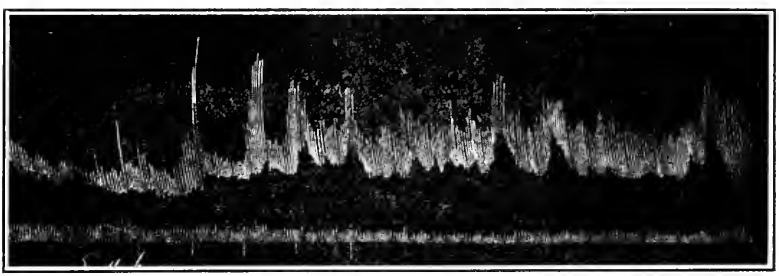

FIG. 4.—Exploratory laparotomy; no lesion found. Upper curve indicates tracing of muscular activity; lower one is the respiratory curve taken from the abdominal wall. Time marked in minutes.

in every normal stomach. These are stronger and more vigorous as well as more rapid contractions, lasting twenty to twenty-five seconds, with a quiescent state of twenty to thirty seconds between each wave. These latter contractions are more variable in their appearance, occurring singly or more usually in groups of two or three contractions. At other times they are vigorous and rapid and may last continually for almost half an hour. We are able to confirm the statement of Cannon that hunger contractions are an indication of the freedom of the stomach from organic disease. The smaller but more constant contractions are an evidence of the tonal variations in the gastric peristole, and bear an important significance for our study.

Turning now to a consideration of the kymographic tracings of diseased stomachs we note that cases of gastric neurosis of some type and vagotonia (Fig. 6) show markedly increased tonic contractions and exaggerated and rapid hunger contractions. On the contrary, those cases of atonic and prolapsed organs show dimin-

ished tonal waves and often absent hunger contractions. In our series, cases of gastric or duodenal ulcer have with only one exception failed to give evidence of hunger contractions. The tonal

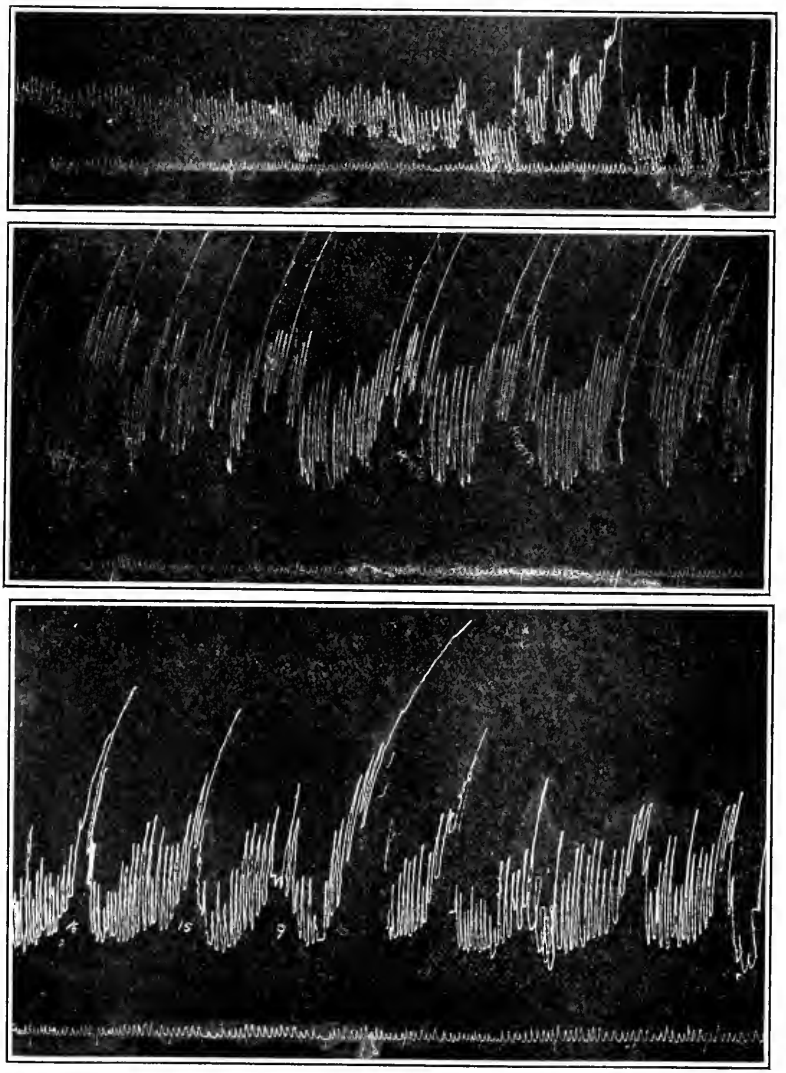

FIG. 5. The same as Fig. 4. The three parts form a continuous record.

waves are retained though often of an irregular and discoördinated variety. Before operation there is no evidence of diminished tone, with the single exception of a case of penetrating ulcer of the lesser curvature in which reflex pylorospasm and inhibition of motility

produced dilatation of the organ; in this case all evidence of any contraction was absent.

Let us now compare the kymographic tracings of cases after operation with the ante-operative curves. We will note that almost all the cases examined within one month after the radical procedure show a complete loss of the peristaltic function of the organ; the curve becomes almost flattened out, a few irregular contractions being present in a smaller percentage of cases. In group A the cases that have become well, 3 cases out of 7, show already good tonal contractions as well as very good hunger contractions shortly after the surgical procedure; a fourth person regains his contractions some time later; 3 of the cases to date have evidenced some sign of returning tonal waves, but as yet no hunger contractions. In group

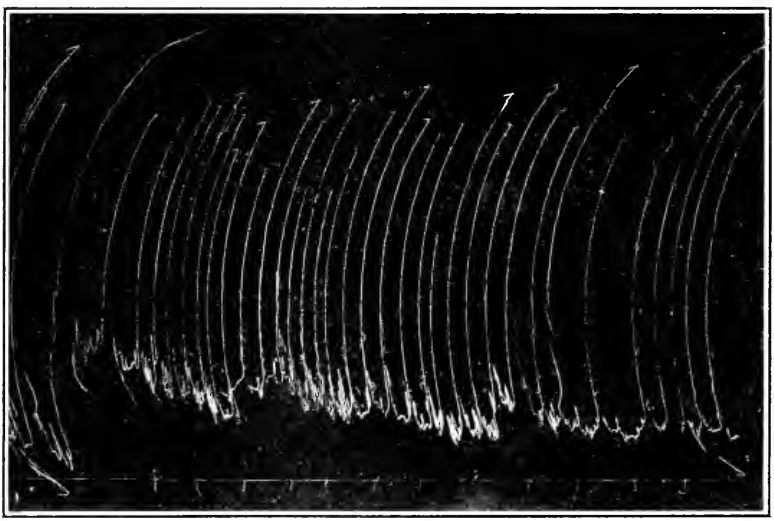

FIG. 6.—Exploratory laparotomy; no lesion found. Diagnosis: vagotonia.

B the cases classed by us as examples of functional disturbance, of 8 cases traced, 4 show poor or no tone (Fig. 8) and 4 only fair tonal contractions. There is no single instance of the more vigorous hunger contractions in this group. As a control we give Fig. 9, which shows the character of tonal wave and hunger contractions in the stomach of a man upon whom exploratory laparotomy had been performed and no disease found.

In group C those cases of organic stenosis of the gastrojejunostomy stoma, of 4 cases traced, 2 retained good and 2 retained fair tonal waves. Hunger contractions are again absent, though we note that none of them can be classed as having poor or absent tonal contractions (Fig. 10).

Thus we see that group B is characterized by the presence of

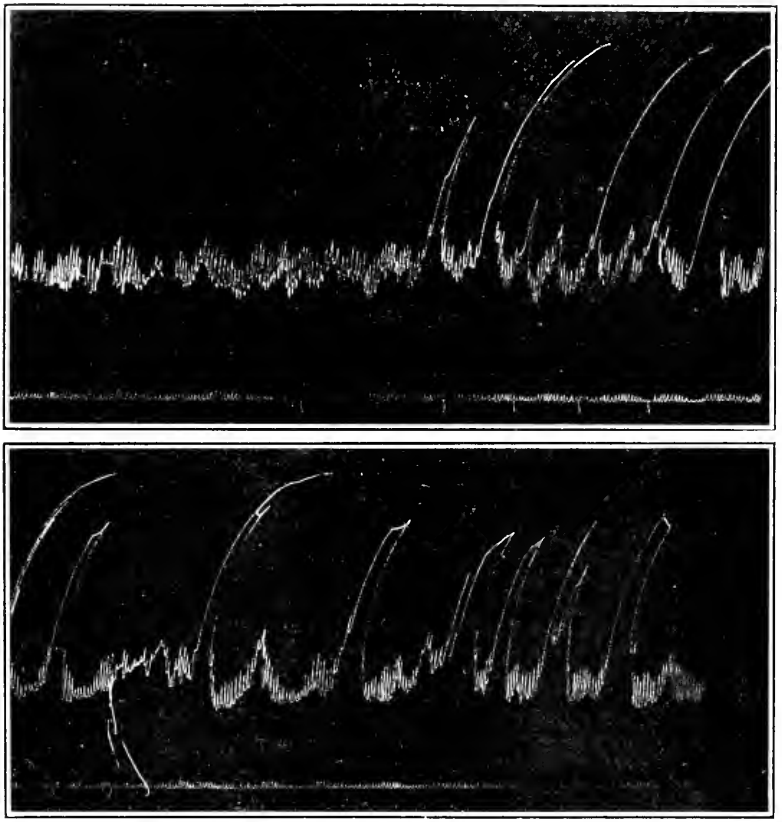

FIG. 7.—Gastro-enterostomy with pyloric exclusion by the string method. Six months after operation; cured case. Type of curve customarily seen in patients having no lesion in the stomach. The two parts form a continuous record.

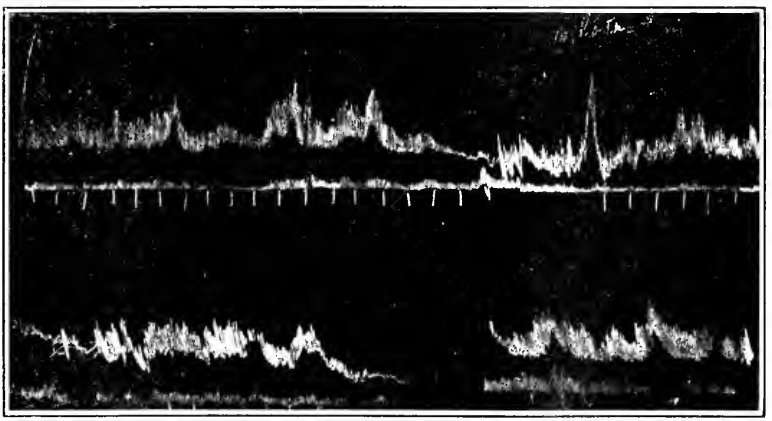

FIG. 8.—Gastro-enterostomy with pyloric plication for duodenal ulcer. Two years after operation; functional disturbances.

only poor or fair tone, and the complete absence of any example of good tonus or hunger contractions. Group A shows fair tone soon after the operation and a regain of normal tone soon after or later after the surgical procedure; it is in this group of practically

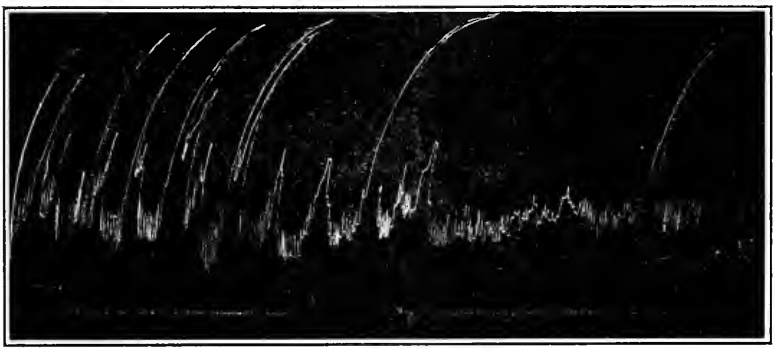

Fig. 9.—Exploratory laparotomy; no lesion found. One month after operation; demonstrating non-interference with the muscular activity of the stomach when the latter is only handled and when no operative procedure is carried out. Compare with Fig. 5 which represents a tracing from the same stomach before operation.

well cases that we see the only return to the normal condition of hunger contractions (Figs. 11, 12, 13, and 14). The organic stenosis cases (group C) retain fair tone but never show hunger waves. Thus, all in all of the 17 cases traced after operation 11 showed definite diminution of tone; only 6 retained good tone.

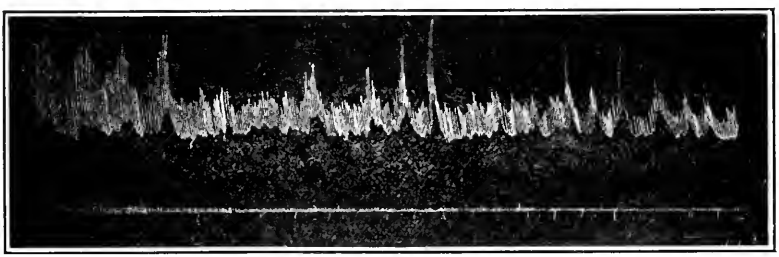

Fig. 10.—Gastro-enterostomy with string exclusion. One year after operation; secondary operation showed narrowing of the stoma and slightly patent pylorus. Curve illustrating muscular activity in the presence of an anatomical obstruction to the egress of the stomach contents.

Radiographic Evidence. This may be summarized as follows: In those cases in which there is return to health (group A, Table III) (11 out of 37) peristalsis is noted as good; there is no residue six hours after the administration of the contrast meal; the stoma is reported as open and functionating efficiently. In the second group (group B, Table IV) those with disturbances of the muscular tonal mechanism as well as of secretory activity the stoma is mentioned

as inefficient in 5 instances of 9 examined, in a sixth case as completely non-functionating. In the other 3 cases the stoma is spoken of as efficient by the contrast meal method of examination. In all of these cases the pylorus is shown to have reopened in spite of

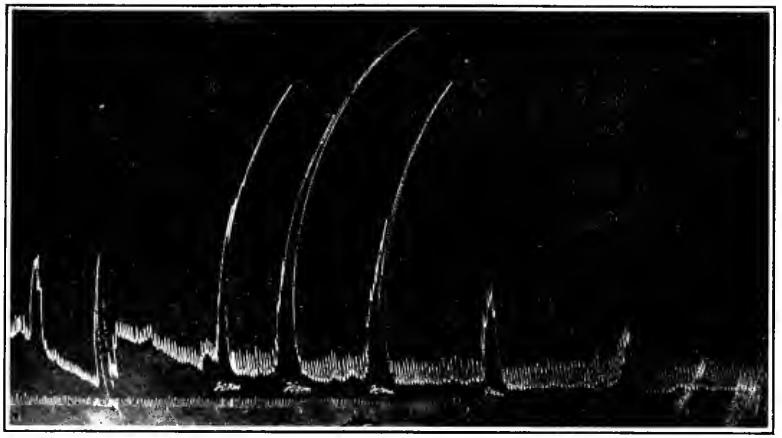

FIG. 11.—Case of duodenal ulcer before operation.

the string exclusion, the earliest case examined being two months after the operative procedure. In all of the instances the peristalsis is described as active or very active, yet in 5 of the 8 cases a bismuth residue is noted after six hours. In the final group C, table V of

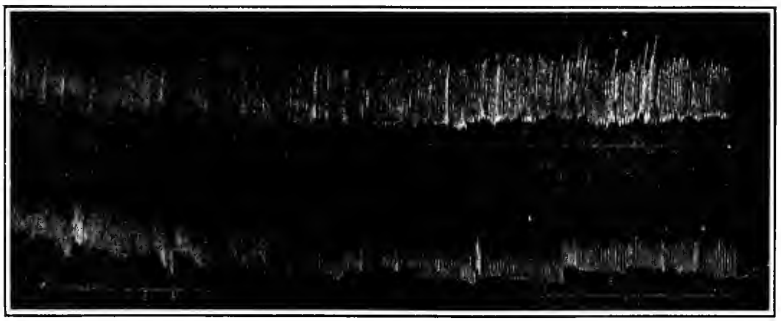

FIG. 12.—Same case as Fig. 11. Four weeks after operation. Kymographic tracing showing almost complete absence of tonus changes and complete absence of hunger contractions.

organic stenosis of the stoma, the stoma is described 3 out of 4 times as inefficient and once as completely obliterated; the pylorus is open in all the cases, only partly open in half of them. Peristalsis is observed three times as violent, once as hyperactive.

In recapitulating the dominant characteristics of these three

groups obtained by the various means at our disposal we will recall the following: 37 cases have been examined to ascertain the functional activity of the stomach after gastrojejunostomy as performed by competent surgeons employing a technic uniformly accepted today.

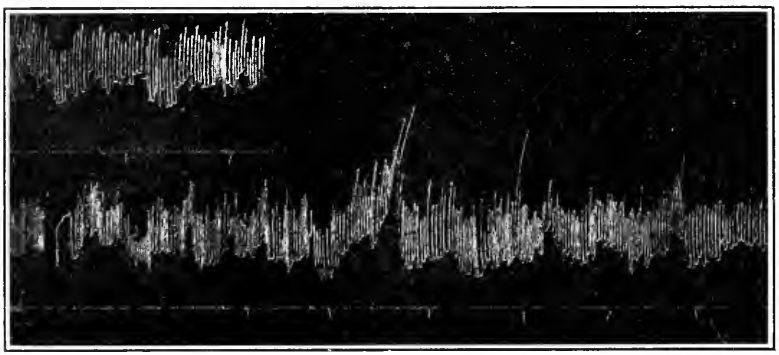

FIG. 13.—Same case as Figs. 11 and 12. Five weeks after operation showing beginning return of tonus contractions and at one point an incomplete attempt at a hunger contraction.

Eleven of these fall into group A. These have all been regarded as well. Clinically they have few trivial or no complaints. Chemical examinations demonstrate a mildly diminished motility after Ewald and Riegel test meals, with diminished acidity and a moderate

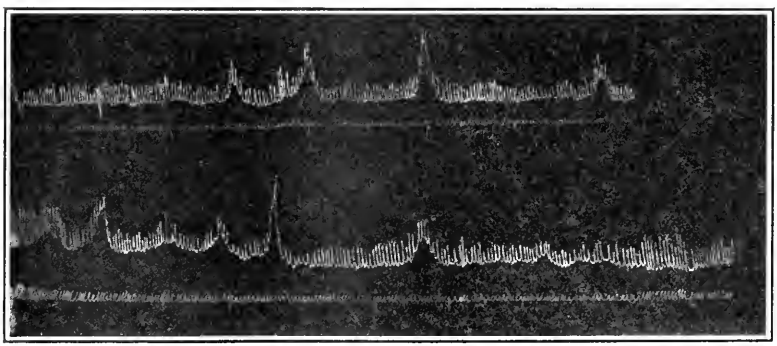

FIG. 14.—Same case as Figs. 11, 12 and 13 now four months after operation. Note the return of the regular tonus contractions of the gastric musculature as also the presence of hunger contractions though not yet in full strength.

but distinct and persistent hypersecretion. The fractional method of Rehfuss shows a nearly normal curve. Kymographic tracings show moderate diminution in the tone, but in about half of the cases a return to the normal occurs very soon. The roentgen ray fails to show a six-hour residue and the stoma functionates properly.

The next 14 cases fall into group B. These cases remain poorly nourished and complain of the following symptoms: pain, vomiting, occasionally hematemesis, constipation, or rarely diarrhea. They are frequently depressed mentally. Chemically, definite delay in motility is shown and hypersecretion is present. The stomata functionate poorly. The kymograph shows either a complete absence or a marked diminution of the peristolic tone and the normal hunger contractions are not regained The radiograph shows the stoma to be functionating improperly and the peristalsis is noted as active or very active. This group is characterized mainly by disturbed muscular function leading to inefficiency of a still patent stoma with definite delay in gastric motility.

The third group comprises 7 cases of organic stenosis of the stoma. Clinically, they resemble the preceding group. Chemically, they show even a greater degree of gastric retention and delayed motility. By the kymograph they may be shown to have regained fair or good peristolic tone. Radiographically, they show violent peristalsis, six-hour residues, and inefficient or closed stomata.

Discussion. The foregoing study must tend to cause us to reconsider our views as to the events taking place after operative procedures upon the stomach. It becomes evident that the impression now very generally in existence that gastrojejunostomy is an operation which in no way impairs the functional efficiency of the stomach is an erroneous one. The operation leaves this organ definitely impaired in a large percentage of the cases. The creation of a new opening in a situation not intended by nature disturbs the peristolic tone of the stomach, the secretory function, and the nervous mechanism controlling both. In only a minority of the cases does the stomach return to an almost normal state of functional activity.

How great a factor artificial pyloric exclusion plays in this disturbance we cannot estimate with any degree of accuracy, though we may suspect it of playing some role. It is well known that the best results after operation have been obtained in cases in which some pathological process has gradually caused a stenosis at the pylorus. Here conditions have been prepared over a long period of time for the proper functioning of an artificial stoma, and when made it acts immediately as a long-sought-for and much-needed exit. The sudden artificial attempt to imitate this causes an uncoördinated muscular activity directed in an improper fashion and is perhaps accountable for at least part of the disturbances seen after such operations.

We must plead with the surgeon sedulously to avoid what has so aptly been called by v. Eiselsberg a "concession operation," by which we understand a gastrojejunostomy in cases in which no definite organic lesion is demonstrable in the stomach at operation. These are the cases which show the greatest amount of disturbance

of function after operation. These cases as well as all doubtful cases ought to be relegated to the medical man, who if he cannot always show the brilliant successes of the surgeon, will by his diligence preserve the patient from some of the unpleasant sequelæ which can readily arise after even a well-judged operation.

We express our appreciation to Dr. A. A. Berg, the head of the gastro-enterological service, for his many courtesies during the course of this work.

This paper is not intended to indicate in any way the percentages of total or partial cures or of recurrences of some or all of the symptoms after operation. The apparent emphasis put upon those cases with recurrent symptoms after operation was purposeful, in that we aimed particularly to investigate the causes for the recurrence of symptoms after operation.

TWO CASES OF PROBABLE SYPHILIS OF THE INTESTINES.

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and
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Approximately 700 cases of syphilis have been under observation either in the wards or in the Outdoor Department of the Peter Bent Brigham Hospital during the past three years. Although a number of these cases have presented interesting lesions, the two cases which we report in this paper we believe to be very unusual. In this series of 700 cases there were 14 individuals who showed lesions of or symptoms referable to lesions of the alimentary tract. This is exclusive of early cases with mucous patches in the mouth and throat and similar lesions about the anus, and also exclusive of those cases, with positive findings in the spinal fluid, having gastro-intestinal symptoms which were due to neurological conditions. Of the 14 cases mentioned above, 9 showed syphilitic lesions recognized as being common: gumma of the tongue 4, gumma of the palate 3, stricture of the rectum 2. In two other cases the gastro-intestinal symptoms were possibly due to syphilis. One, a woman, three months pregnant with a ++++ Wassermann reaction, complained of persistent vomiting which cleared up with rest in bed, light diet, and two doses of salvarsan. A second case with a ++++ Wassermann reaction complained of pain and burning in the epigastrium and had a positive guaiac test in the stools. Operation disclosed nothing in the stomach or duodenum which would explain the symptoms. She

was given no antisyphilitic treatment, and it has been impossible to get in touch with her since she left the hospital. What influence, if any, syphilis had in these two cases it is not possible to say. Another case with a ++++ Wassermann reaction complained of vomiting and loss of weight, and bismuth roentgen-ray examination suggested carcinoma of the stomach. Under intensive antisyphilitic treatment for one month the patient gained in weight, but as repeated bismuth roentgen-ray studies showed no change in the stomach, laparotomy was done. A diagnosis of syphilis of the stomach was made at operation. The remaining two cases of the group of 14 we will consider in detail as probable cases of syphilis of the intestines.

CASE I.—J. P. N. Medical No. 25. White; male; single; born in Ireland thirty-two years ago. Entered the hospital April 14, 1913, complaining of bloody diarrhea.

Family History. One sister died of pulmonary tuberculosis seventeen years ago. Just before her death she developed a bloody diarrhea. A second sister died of pulmonary tuberculosis thirteen years ago. A third sister died of the same condition seven years ago and developed a bloody diarrhea before death. An only brother died of pulmonary tuberculosis three years ago. Patient was not immediately exposed to infection from any of these cases. Father is living and well. Mother died seven years ago after an operation for intestinal obstruction.

Past History. Patient has not lived outside of the New England States and New Brunswick, Canada, since he came to America, twenty-five years ago. He has always worked as a harness-maker. He uses alcohol to excesss and periodically gets drunk. He had scarlet fever in youth, but gives no history of tonsillitis, rheumatic fever, chorea, pleurisy, pneumonia, malaria, or serious injury. He has had gonorrhea three times; the last attack was four years ago. Fourteen years ago, without any previous local lesion, he had a rash which covered his face, body, and hands. There was no itching. A few days later he developed sores in his mouth and a sore throat. He was treated with mercury by mouth for four months, but has had no antisyphilitic treatment since. Twelve years ago he was treated at Rutland, Mass., for pulmonary tuberculosis. During the five months there he gained 47 pounds in weight. He is not sure, but thinks that tubercle bacilli were found in his sputum on one examination. After leaving Rutland he went down to his former weight of 140 pounds and has remained at that figure up to the present illness.

Present Illness. Duration seven years. In the summer of 1906 he developed a bloody diarrhea averaging ten to eleven bowel movements daily. These were very loose and bright yellow, and were mixed with dark blood at times and often covered with bright, fresh blood. At various times he passed pure blood alone and small strings of mucous membrane with the blood. The first attack of these

symptoms lasted three and a half months. There were severe griping pains in the abdomen, worse before and just after defecation. He lost 7 pounds in weight. The attack passed off gradually. He had an attack of the same character of only three days' duration during the following winter. The next summer, 1907, he had a second severe attack which lasted two and a half months, during which he lost 3 pounds. The following winter he had a third severe attack of five months' duration. During this attack he went to the Bar Harbor Hospital, where he remained three weeks, and under a restricted diet and medicine by mouth the symptoms gradually cleared up. Since that time, six years ago, he has had repeated attacks which come at intervals of about six months, and which last from six to eight weeks. The present attack began six months ago and has been similar to those described above, except that it was more severe. In the last two weeks he has lost 10 pounds in weight. He has no cough, raises no sputum, has no cardiac or renal symptoms, and no neurological disturbances, except that he is nervous about his present condition.

Physical Examination. Temperature 98.6°, pulse 80, respiration 22. Patient is a well-developed and fairly well-nourished man lying flat in bed and apparently comfortable. Skin: negative except for slight acne over shoulders and back. Glands: epitrochlear, cervical, and inguinal; are palpable, but not markedly enlarged. Eyes: an irregular corneal scar due to trauma causing an irregular and fixed pupil is present on the right; the left pupil reacts to light and accommodation. Tongue, teeth, and mouth are essentially negative. Thyroid not enlarged. Chest is long and narrow, with some flattening of the right side anteriorly. Lungs: negative findings. Heart: negative findings. Pulses: equal and regular. Blood-pressure: systolic 130, diastolic 60. Abdomen: in the lower right quadrant the individual loops of intestine are easily made out through the belly wall and are slightly tender to firm pressure. No masses are felt. Liver not enlarged and the edge is not felt. Spleen not felt. Extremities negative. Reflexes: deep and superficial are present and equal on the two sides.

Laboratory Examinations. Urine: clear; acid; specific gravity 1018; no albumin; no sugar; sediment negative. Blood count was as follows: hemoglobin 70 per cent., white blood cells 12,200 per c.mm., polynuclear neutrophiles 57 per cent., lymphocytes 38 per cent., eosinophiles 5 per cent. Wassermann reaction ++++. Spinal fluid: cells 2 per c.mm.; globulin (Noguchi) negative; positive Fehling's test; Wassermann reaction negative. Stool examination showed blood and pus mixed with much mucus; no food residue. Many examinations failed to show amebæ, tubercle bacilli, ova, and parasites. Guaiac test was strongly positive.

Bismuth Roentgen-ray Examination. No evidence of gastric or duodenal ulcer; some ileal and cecal stasis, a bismuth residue in the

ileum after nine hours and in the cecum after thirty hours. Roentgen ray of chest: no evidence of tuberculosis. There is a slight increase in the density of the shadow around the root of the right lung.

Proctoscopic Examination. There is considerable tendernesss on insertion of the proctoscope and marked pain on slight inflation. Nothing abnormal seen at the sphincter margin. The mucous membrane of the rectum is definitely hyperemic and there is a surface coating of bloody purulent mucus which can be wiped off, leaving a granular looking surface epithelium which shows evidence of some superficial desquamation. There are no discrete circumscribed ulcers made out, but there are numerous small hemorrhages in the mucous membrane. Apparently the rectal wall is thicker, firmer, and more rigid than normal, and gives one the impression of a leathery consistency. The longer sigmoidoscope reveals much the same condition in the lower sigmoid. Smears made from the wall of the bowel are negative for tubercle bacilli.

For approximately three weeks the patient's condition remained as at entrance. Stools similar to the admission specimen were passed from six to eight times daily. Temperature continued normal; pulse averaged 70; respirations 20. Irrigating fluids were varied from warm normal salt solution to 1 to 1000 silver nitrate. Patient stated that all of these irrigating fluids and many more had been tried in previous attacks without effect.

Three weeks after admission, treatment with neosalvarsan was begun. In the week following the second injection the stools averaged two daily, and were yellow brown with an excess of mucus. Occasionally fecal masses were found with some undigested food and occasional streaks of blood. Examinations for tubercle bacilli done approximately twenty times were always negative. Neosalvarsan was continued at weekly intervals.

June 3, seven weeks after admission and one month after the first dose of neosalvarsan, proctoscopic examination was repeated by the same observer. Mucous membrane of the lower rectum reveals a thin coating of pinkish-brown mucus which can be easily wiped away. The underlying mucous membrane is less hyperemic than on previous examinations, but the surface is still somewhat granular in appearance. There are no definite ulcerations. The small punctate hemorrhages that were seen before have disappeared. On the whole there has been marked improvement. The mucous membrane is less injected and less roughened. No free blood is present anywhere. The tenderness and discomfort after the previous examination were not noticed this time.

Patient was discharged from the hospital June 9 after a total stay of fourteen weeks. During the last three weeks he averaged only one movement a day. Improvement in his general condition was marked. He gained weight, his appetite improved, and he felt stronger and better in every way, and had no discomfort on going to

stool. Hemoglobin rose from 70 to 90 per cent. A stool examined on the last day of his stay in the hospital was large, well formed, dark brown, without mucus or blood; microscopic examination negative; guaiac test faintly positive. The total amount of neosalvarsan given was 4.2 grams.

For eight months after leaving the hospital the patient was lost track of. A letter was received from him February 3, 1914, saying that symptoms of his former trouble were reappearing. He was readmitted February 28, 1914. At this time he stated that for six months after leaving the hospital he was perfectly well. About Christmas he noticed a beginning frequency of defecation, which rapidly grew worse. Blood began to reappear in his stools, and he noticed severe griping pain in the lower abdomen. At present he is having eight to ten movements daily. He is weak, tired, somewhat worried and nervous, has many headaches, and does not sleep well. Physical examination shows no points of difference from that of first admission. Stool: brown; semifluid; no parasites or ova; slight amount of mucus and few blood streaks; no tubercle bacilli. Wassermann reaction ++++ in the serum.

Sigmoidoscope Examination. Slight tenderness on insertion and very little pain on inflation. There is a great deal of mucopus and free blood in the lumen of the bowel, and the mucous membrane everywhere seems coated with the same material. This is readily wiped away, leaving a very injected granular surface which shows many punctate hemorrhagic spots and bleeds at a touch. There are no definite ulcers.

Bismuth Enema and Roentgen-ray Examination. Examination of the colon shows a normal configuration of the cecum, ascending colon, transverse colon, splenic flexure, sigmoid flexure, and rectum. The lower aspect of the descending colon shows abnormal findings. The bismuth enema stops for a few minutes on reaching this point, afterward it passes the descending colon abnormally quickly and no complete filling of this part of the colon can be demonstrated. This is very likely due to spastic contractions of the wall of the descending colon. The upper portion of the descending colon as well as the rest of the colon shows a broad normal filling. The enema does not pass the ileocecal valve. Bismuth given by mouth shows a normal transport as far as the upper portion of the colon. After three days, in spite of several movements, a definite stasis in the descending colon is seen.

Salvarsan, 0.3 gram, was given March 3. No improvement resulted in the number or character of the stools during the next ten days. A second dose of 0.5 gram was then given, and almost immediately the number of stools per day fell to two, and on March 18 the stool is described as formed, brown, streaked with blood, with a small amount of mucus. Guaiac test positive. Bismuth roentgen-ray examination was repeated March 21. About

fourteen hours after the bismuth meal a complete filling of the cecum, the ascending and transverse colon is to be seen as far as the splenic flexure. There is no evidence of stasis at the upper portion of the descending colon, as on previous examination. In the middle of the descending colon, however, one haustrum shows an unusual amount of gas. The examination the following day shows a considerable amount of bismuth scattered out in the entire colon. There is a considerable amount of gas to be seen in the descending colon. A bismuth enema fills the entire colon as far as the cecum without any hindrance. He left the hospital at the end of a three weeks' stay, but was readmitted several times during the following weeks for additional salvarsan treatment, staying in the hospital for only twenty-four hours. The salvarsan given totaled 4.8 grams. The last dose was May 23, 1914. He was again seen October 23, 1914, at which time he reported that he was perfectly well. On one or two days he had had loose movements, but he had passed no mucus, pus, or blood. June 20, 1915, a letter was received from St. Johns, N. B., where he now lives: "I am in good physical condition, working thirteen hours a day. My weight is within 4 pounds of normal. One month ago I had an attack of diarrhea lasting about one week and passed fresh red blood and undigested food, but this soon cleared up without any treatment. At times feces when very firm are ribbon-shaped and are passed with difficulty. This does not seem to be growing worse."

Differential Diagnosis. In this case we believe that malignant disease can be ruled out on the duration alone, eight years. The diagnosis evidently lies between syphilis and tuberculosis. The latter we have discarded as a probability because of the absence during the three years while under our observation of all signs of active tuberculosis elsewhere either by physical or roentgen-ray examination; the absence of signs of active tuberculosis elsewhere on repeated physical examinations at other hospitals; sputum always negative for tubercle bacilli; absence of fever, rapid pulse, and night sweats; loss of weight was always proportional to the diarrhea; stools were always negative for tubercle bacilli; smears made directly from the wall of the bowel were negative for tubercle bacilli on three occasions; extreme chronicity.

We consider it proved that the patient has syphilis because of the history of infection, the general adenopathy, and the persistently strongly positive Wassermann reaction. We also believe the condition to be syphilitic because of the tendency to spontaneous healing, the distinct improvement locally, and in the general condition of the patient following neosalvarsan the relapse followed by definite and more lasting improvement under salvarsan, inefficacy of other forms of treatment, present excellent general condition of the patient, and the absence of symptoms of local active disease.

CASE II.—R. D. A. Medical No. 3486. Negro; male; single; born in North Carolina twenty-nine years ago. Admitted to the hospital October 19, 1915, complaining of stomach trouble.

Family History. Father, mother, six brothers, and three sisters are living and well. Three sisters died in infancy of unknown cause. No history of hereditary or contagious diseases in the family.

Past History. Patient worked as a machinist up to six years ago; since then he has worked as a hotel waiter. He had measles, mumps, whooping cough, and occasional attacks of tonsillitis as a child. There is no history of other diseases or of any injury. No cardio-respiratory symptoms. Ten years ago he had two attacks of severe vertigo which lasted three or four minutes, but has had none since. There have been no neuromuscular symptoms, no fainting spells, spasms, disturbances of sensation, ataxia, girdle, shooting or muscle pains. He had gonorrhea four years ago, followed by no complications. Six years ago he had a hard genital chancre which was treated with mercury by mouth. There was no rash, no sore throat or sore mouth, and no loss of hair following this primary lesion. One year ago he had an enlarged inguinal gland which was opened and drained at this hospital. Nine months ago his best weight was 185 pounds, and he lost no weight up to the onset of the present trouble. Appetite was always good and he could eat anything. Bowels were usually regular. He never had nausea, flatulence, vomiting, hematemesis, colic, jaundice, diarrhea, or abnormally colored stools. During the past year he has had some trouble from external hemorrhoids.

Present Illness. Two weeks ago, while going home from work, he suddenly became nauseated and vomited. The vomitus was not of large amount or dark colored, and contained no blood. He had no pain at any time. During the next few days he continued to work, but he vomited once or twice daily. Three days after the first attack of vomiting he noticed colicky pain in the epigastrium; this pain did not radiate and was not related to meals, but was worse between 6 and 8 P.M. and between 2 and 3 A.M. The pain was not relieved by food, and no food would stay down. He had considerable belching of gas, which was partially relieved by soda and ginger. One and a half weeks ago he gave up work and went to bed. In a few days the pain and vomiting ceased and he went back to work. Two days ago the pain and vomiting recurred, forcing him again to stop work. During the last day the vomitus was black in color. He was markedly constipated. His stools have not been of abnormal color. He has had no chills or fever, no cough, dyspnea, edema, or palpitation.

Physical Examination. A well-developed but poorly nourished young negro lying comfortably in bed. Skull, scalp, and skin show nothing of interest. Eyes: pupils are equal and regular, reacting well to distance. To light they sharply contract and then dilate.

There is no photophobia, lacrimation, nystagmus, ocular palsy, lid lag, or exopthalmos. No disturbance of vision. Ears: deafness on the left side, normal hearing on the right. Mouth: marked pyorrhea; no ulcerations and no bleeding. Glands: epitrochlears are palpable on the two sides; several cervical glands are palpable in the posterior triangles; the inguinals are palpable on both sides, and there is a healed scar of an old incision for bubo on the left. Thorax is well developed and symmetrical, with good and equal expansion on both sides. Lungs: good resonance and fremitus and normal breath sounds throughout. Heart: no abnormalities are made out in size, impulse, or sounds. Blood-pressure: systolic 106, diastolic 68. Abdomen is symmetrical, level, and tympanic throughout. No masses are felt. There is slight tenderness on palpation in the epigastrium. Upper border of the liver is at the fifth rib; the edge is not felt. Spleen is not palpable and not enlarged to percussion. Kidneys are not felt. Reflexes: palate reflex is present, the cremasteric and abdominal are greater on the right than on the left. The biceps, triceps, radioperiosteal, knee, and Achilles reflexes are not obtained on either side. There is failure to bring the forefingers of the hands together accurately with the eyes closed, but the finger-to-nose and the heel-to-knee tests are well performed. There is no ankle clonus and no Kernig sign present. Gordon and Oppenheim reflexes are negative. Romberg test slightly positive. Sensation is nowhere impaired. Rectal examination: no hemorrhoids; no stricture; prostate is not enlarged or tender; no masses are felt and there is no blood on the examining finger. Temperature 98°, pulse 80, respirations 20. Weight 70.6 kg.

Laboratory Examination. Urine: amber; acid; clear; specific gravity 1029; no albumin; no sugar; no acetone; no diacetic acid; no bile present. The sediment is negative. Blood: hemoglobin 92 per cent., white blood cells 7300 per c.mm. Polynuclear neutrophiles 77 per cent., lymphocytes 23 per cent., no eosinophiles and no basophiles seen. Red blood cells 5,000,000 per c.mm. Wassermann reaction ++++. Spinal fluid: clear; 8 lymphocytes per c.mm.; globulin (Noguchi) negative; positive Fehling's test; Wassermann reaction negative with 2 c.c. Stool: dark, tarry, and soft; several large masses of mucus are present. Guaiac test is positive. Microscopically many red and white blood cells are present, no ova and no ameba found. Vomitus: 100 c.c. of dark brown material with gross food particles and much mucus; guaiac test positive. Gastric contents on fasting: 70 c.c. of greenish-yellow fluid with some well-digested food residue and much mucus. Microscopically a few red blood cells and epithelial cells and some starch and fat noted; no sarcinæ or Boas-Oppler bacilli found. Free HCl absent, total acid 22; guaiac test positive. Test meal (Ewald one hour): 100 c.c. of a pale green fluid with much well-digested food residue but no mucus. Guaiac test negative. Microscopically much starch and fat.

Roentgen-ray Examination. Standard bismuth meal given at 6 A.M. At 10.30 a large trace remained in the stomach, the lower ileum was filled and a small amount was present in the ascending and transverse colon. After a special mixture of malted milk, corn starch, and 90 grams of bismuth subcarbonate the stomach was negative; the pylorus and duodenum were regular in outline. At 9.30 A.M. the following day there was a small residue in the terminal portion of the ileum, indicating ileal stasis; the larger part of the residue was in the descending colon. At 12.30 on the third day a bismuth enema showed the sigmoid to be very redundant, one loop reaching the height of the splenic flexure. When completely filled the splenic flexure was parallel with the descending colon. Roentgen-ray of the chest showed negative findings.

For two days he was given cracked ice and small amounts of milk. Bismuth studies were begun on the fourth day and lasted for three days, as noted above. October 24 the patient was put on a Lenhartz diet and five days later additions to this diet were made. The temperature, pulse, and respirations continued normal. The stools continued to show blood, mucus, and occasional pus cells. His weight fell to 66.7 kg. During the next two weeks there was no change in the patient's condition except that he was having less epigastric pain and fewer attacks of vomiting. At the end of this period of two weeks diarsenol, intramuscular mercury, and potassium iodide were begun. Four days after the first dose of diarsenol all pain and vomiting ceased. He was put on house diet, and for the first time since admission the stools gave a negative guaiac test, and this was repeatedly negative during this admission. He began to gain weight, and in ten days he had gained 3.5 kg. A total of 1.4 grams of diarsenol intravenously, 1.3 grams of succinimide of mercury intramuscularly, and 20 grams of potassium iodide by mouth was given. He was discharged November 16, 1915, and since then has been under antisyphilitic treatment in the outdoor department. February 18, 1916, three months later, he was still free from symptoms and had gained 10 kg. in weight. A stool specimen showed no mucus, pus, or blood, and gave a negative guaiac test.

In this case the history of a primary sore and the general adenopathy and strongly positive Wassermann reaction in the serum made us certain that the patient had syphilis. The failure to improve under light diet and rest and the remarkable improvement under antisyphilitic treatment indicate that syphilis was the cause of the condition which he presented.

It seems impossible to localize the lesion which caused the symptoms; however, we believe that the bleeding was not of gastric origin, since no blood was noticed in the vomitus until two days before entrance, although he had vomited repeatedly. The blood-stained vomitus was observed only after persistent and continuous vomiting. Following the emptying of his stomach, at which time the

fluid gave a positive guaiac test, he was given a test meal which on removal one hour later gave a negative guaiac test. The stools contained well-preserved red blood cells, pus cells, and mucus. Bismuth roentgen-ray showed no evidence of ulceration in the stomach or the duodenum.

No systematic attempt has been made to review the literature on this subject, but all the standard medical and surgical text-books, including the various systems of medicine, surgery, and syphilis, have been consulted. The opinion is uniformly expressed that syphilis of the stomach is uncommon and that syphilis of the intestine is extremely rare.

DIVERTICULUM OF THE DUODENUM, WITH A REPORT OF A CASE DIAGNOSED DURING LIFE AND SUCCESSFULLY OPERATED ON.[1]

By Seymour Basch, M. D.,

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Diverticulum of the duodenum is a rare condition and one not well known to the profession in general. It has no characteristic clinical symptomatology and, until the most recent advances in radiological diagnosis, its presence was revealed only during a postmortem examination. The writer therefore feels that the following case, diagnosed during life and successfully operated on, is of sufficient interest to be herewith reported.

Case History.—J. L.; female; single; aged thirty-six years; fire insurance agent. Referred by Dr. S. Rosenberg. Patient was first seen by me January 5, 1915, when she gave the following history:

Her family were all rheumatic and very nervous; her mother and one brother died of heart disease. She was left very much to nurses, her dietary neglected, and she remembers that she was a weak, anemic child, very constipated, and often troubled with indigestion. She had had no acute illnesses since childhood, though always thin and pale. Her constipation has persisted despite manifold measures and drugs, and she has often passed large amounts of thick, ropy mucus, with or without feces. In addition, since childhood, she has been troubled more or less with "sour stomach" (heartburn, acid belching, distention, flatulence, etc.), particularly after

[1] Read at the Nineteenth Annual Meeting of the American Gastro-enterological Association, at Washington, D. C.

partaking of sweets, acids, fruits, etc. At times there was even an aching pain in the upper right quadrant, coming on about one hour after meals. These manifestations of gastric indigestion always yielded to strict attention to diet. For years she was troubled with hemorrhoids and rectal fissure, being finally cured, after several previous operations, three years ago by Dr. Kelsey. Six years ago she was operated on for appendicitis at St. Mary's Hospital in

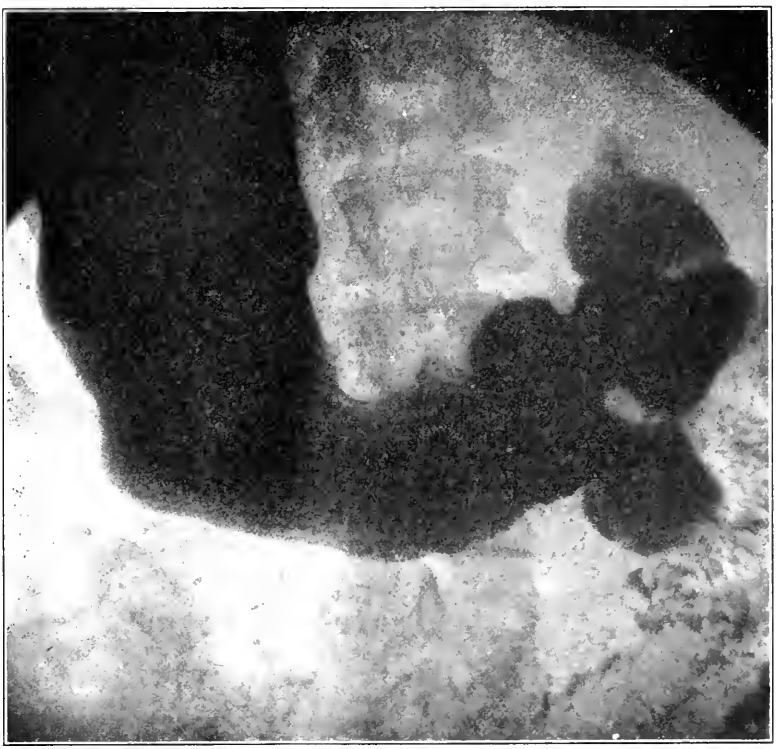

FIG. 1.—Taken prone a few minutes after the bismuth meal. Stomach very active, duodenal cap normal. Note the large round, bismuth-filled pouch between the second portion of the duodenum and the pyloric antrum, apparently communicating with the latter.

Brooklyn. The appendix, she was told, was "large and inflamed, and contained a little pus." Her indigestion, however, was not relieved by any of these operations; on the contrary, it has become progressively worse, and since several months has been particularly distressing despite most careful dieting and medicinal measures. A most annoying symptom has been a sharp, aching pain below the gall-bladder region, occurring one or two hours after meals and lasting for some time.

Status Presens. The patient is very emotional, voluble, and decidedly self-centered; she is thin and pale and appears to be very distressed. The central nervous system is negative, excepting for exaggerated knee-jerks; there are no obvious signs of hyperthyroidism. The pulse is slightly accelerated, soft and regular; blood-pressure is 150 systolic and 95 diastolic. The heart examination reveals a loud aortic stenotic murmur.

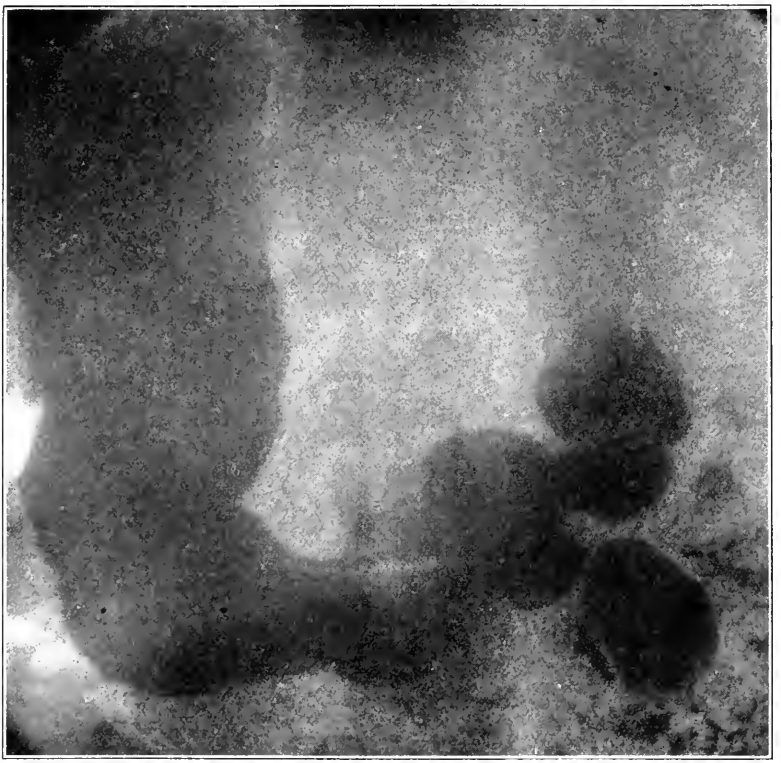

FIG. 2.—Taken erect immediately after Fig. 1. The bismuth-filled pouch occupies the same position, but is seen to be entirely separated from the stomach.

The abdomen is of the enteroptotic type, with a colonic bulge; the right kidney is displaced down to the iliac crest while the left one is ptosed to the second degree. The spleen and liver are not palpable. There is an old firm appendix scar. The gall-bladder region is very tender to pressure, the pain being referred to the right nipple. There is a definite stomach splash, with the greater curvature apparently slightly below the umbilicus.

The feces are soft and bulky, not formed, have a sour odor and strong acid reaction; they show poor starch digestion and are intermixed with a large amount of thick, ropy mucus. Occult

blood is absent and the bile reaction is normal. In the fasting state the stomach is empty, and one hour after Ewald-Boas' breakfast, 2 ounces of contents were aspirated, evidencing no special variation from the normal, and giving 28 free HCl and 60 total acidity.

From the above data the case was regarded as one of chronic inflammatory disease in the gall-bladder-duodenal region, the exact nature of which could not be stated. Chronic duodenal ulcer with possible gall-bladder involvement or adhesions seemed most probable.

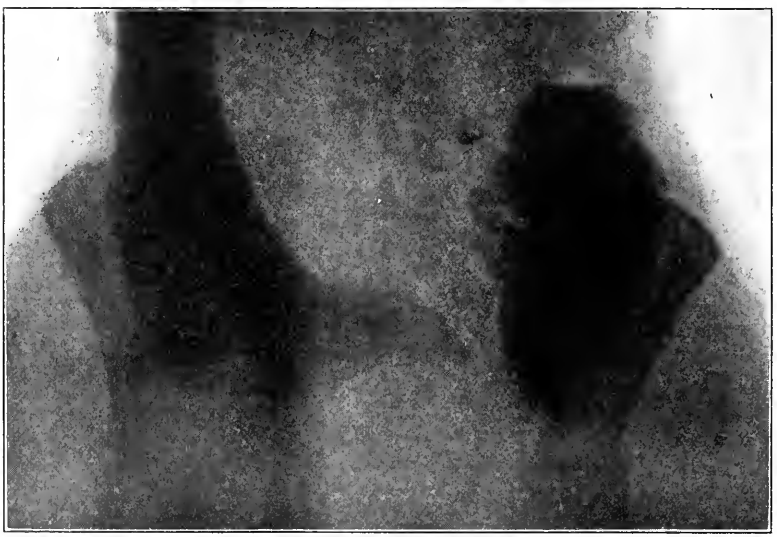

FIG. 3.—Colon enema plate taken ninety-six hours after Fig. 1. There is still a definite though slight amount of bismuth in the duodenal pouch.

January 18, a gastro-intestinal roentgen-ray examination, made by Dr. Arthur S. Unger, gave the following results: The stomach is normal in shape, size, and position; its peristalsis is very active, and it is completely empty within six hours. The bublus duodeni is large and appears overfilled; the cap is normal in contour; part of the first and second portions of the duodenum appear to adhere closely to the liver. Near the commencement of the third portion of the duodenum a distinct bismuth-filled dilatation is seen. It is round and pouch-like in shape and seems to communicate with the duodenum. Serial plates show bismuth retention in this pouch for at least ninety-six hours. In view of these roentgenological findings, the long-standing nature of the case, its resistance to medical therapy, and the recent aggravation of the subjective symptoms, surgical intervention was regarded as the only possible means of relief.

The patient was operated on by Dr. Charles A. Elsberg, January 31. The following was Dr. Elsberg's account of the operation:

An incision of 10 cms. was made through the right rectus. When the peritoneum was opened the pylorus and first and second portions of the duodenum were found to be congested and bound together by numerous fine adhesions. There was no evidence of an ulcer of

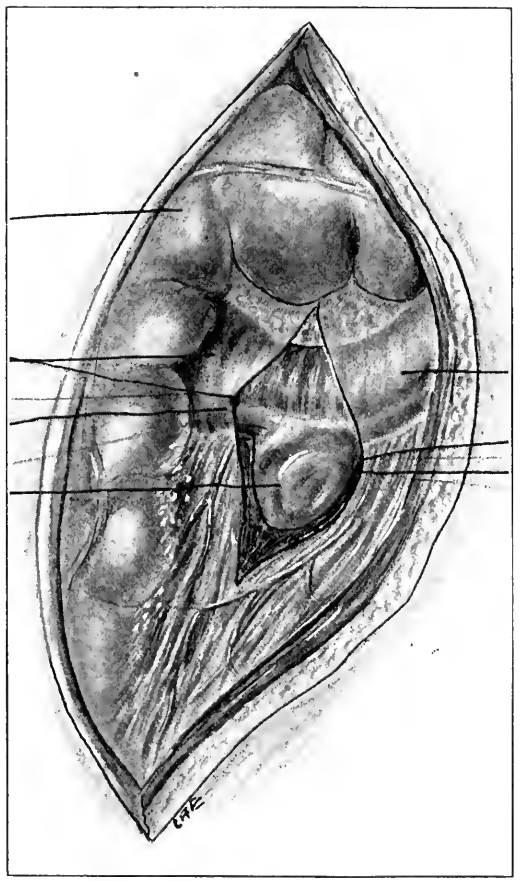

FIG. 1.—Congenital diverticulum of the duodenum at the junction of the second and third portions.

the stomach or the duodenum. The colon was then turned upward the posterior layer of the transverse mesocolon incised, and the third portion of the duodenum exposed. On the lower margin of the duodenum at the angle between the second and third portions was a large diverticulum measuring about 3 x 4 cms., its base about 3 cms. in diameter. The second portion of the duodenum was mark-

edly dilated and hypertrophied, while the third portion was normal in size. The diverticulum was excised at its base in the longitudinal direction, and the opening in the duodenum closed in the transverse direction by a double layer of fine silk sutures. The posterior layer of the mesocolon was then closed by catgut sutures being attached to the suture line and the duodenum. There was no narrowing of the duodenum as a result of the suture. A typical posterior gastro-enterostomy by suture was then performed and the abdomen closed in the usual manner.

The gastro-enterostomy was made because of the periduodenal adhesions and the duodenal dilatation.

The specimen was examined by Dr. E. P. Bernstein, who reported as follows:

Macroscopically the specimen is an intestinal pouch about 3 x 3 x 4 cms., with very thin walls.

Microscopic examination shows the peritoneal coat to be intact and normal; the muscular layer is intact but very thin throughout the entire specimen. The mucous membrane shows numerous defects with loss of the entire mucosa. Where, however, the mucous membrane is present it is normal in character and shows no inflammatory reaction, either acute or chronic.

Diagnosis. We must consider this specimen to be a congenital diverticulum. The loss of mucosa in spots is an artefact.

The patient made a good primary recovery from the operation, and in the short time that has elapsed shows a decided improvement in her digestion. However, in view of the presence of the extensive adhesions, the greatly dilated second portion of the duodenum, the marked enteroptosis, the obstinate constipation, the aortic lesion, and the highly neurotic condition of the patient, anything approaching a complete restoration to health is not to be expected.

This very unusual case is as far as I can learn from an exhaustive study of the literature only the second one to have been diagnosed during life and successfully operated on. The first case reported was one by Forssell and Key[2] in 1915. In their case the location of the diverticulum and the roentgen-ray and operative findings were very similar to those in the one herewith reported. Their patient also had suffered for many years from symptoms of duodenal ulcer. Forssell and Key state that their patient was entirely free from her symptoms after the operation.

It is unnecessary to enter here into any extended discussion of the subject of duodenal diverticulum. Those interested are referred to the writings of Buschi,[3] Bauer,[4] Wilkie[5] and others mentioned in the appended literature. A few remarks intended to

[2] Nord. Med. Arkiv., Stockholm, 1915, Afd. II (Inre Medicin.), Heft. 1, No. 2.
[3] Virchows Arch., 1911, Bd. xxvi, S. 121.
[4] Wien. klin. Wchnschr., 1912, Nr. 23, S. 879.
[5] Edinburgh Med. Jour., September, 1913.

bring out the main points of general interest on the subject may be permitted.

As already stated, duodenal diverticula are of comparatively rare occurrence. There are only between 65 and 70 cases altogether reported in literature. Undoubtedly, the condition is much more frequent than these figures leave one to conclude, for it is easily overlooked unless specially sought for.

According to Buschi, from whose comprehensive study, in 1911, the following facts have mainly been gathered, Chomel,[6] in 1707, reported the finding of a duodenal pocket containing 22 stones at an autopsy on a woman, aged eighty years. This patient, Chomel stated, had always felt a pain at the site of the sac about two hours after meals. Morgagni,[7] in 1839, however, gave the first real description of a duodenal diverticulum.

Duodenal diverticula have been found twice as often in the bodies of males as in those of females, about 80 per cent. of them in individuals over fifty years of age. Over 75 per cent. of the diverticula were located in the second portion of the duodenum, and more especially in the region of the papilla of Vater, and of the opening of the duct of Santorini; hence, the French designation of "diverticules perivateriens." Of 44 cases tabulated by Buschi, the second portion of the duodenum was involved 33 times, the first 6, the third 3, and first and second in the same individual twice. In most instances only one diverticulum has been found in a case, although as many as five have been reported. Thus, Buschi found 35 cases with a single diverticulum, 13 with two, 2 with four, and 2 with five diverticula. The shape varied, being usually spherical or hemispherical; it may, however, be ovoid or like a gloved finger.

In size these pouches range from a few millimeters to 5 cms. in their greatest diameter. The opening may be narrower, but usually is fully as wide or even wider than the cavity of the sac. In a few instances a valve-like fold has been seen at the opening. The width of the opening and the shallowness of the pouch prevent the disastrous consequences so common in Meckel's diverticulum and the vermiform appendix.

The sac has generally been found empty and flaccid; at times, however, it has contained fluid or food remnants, or even stones.

Most investigators report the sac wall as being composed entirely of mucous membrane and submucosa, the mucous membrane being smooth, thin and free, or almost free, from glands. The muscular layer is said to be absent or to appear only as a ring about the opening of the pouch. Buschi, Voelker,[8] Seipel[9] and others,

[6] Histoire de l'Acad. royale, Paris, 1710.

[7] De sedibus et causis morborum, etc., Firenze, 1839.

[8] Beiträg zur Kenntnis d. falschen Darmdivertikeln, Inaug. Dissert., Freiburg, 1906.

[9] Ueber erworbene Darmdivertikel, Inaug. Dissert., Zürich, 1895.

however, found perfectly normal mucosa and some muscle bundles which extended far into the sac, in some instances even to the distal end, being then very atrophic. In our own case the pathologist reports that "the muscular layer is intact, but very thin throughout the specimen."

Diverticula occur only exceptionally on the outer or anterior surfaces of the duodenum; in most instances they are on the inner aspect in contact with the head of the pancreas, from which they are separated by loose connective tissue. Frequently they indent the head of the pancreas, or are intimately connected with the common bile duct or the duct of Wirsung, which usually lie behind the diverticula.

The question of the origin of these diverticula has given rise to much discussion and to a number of interesting theories. Those interested in the details are referred to the papers of Buschi, Wilkie, and Davis,[10] in which the question is gone into at length. Buschi himself concludes that they are to be regarded as of congenital origin, and gives detailed reasons for his conclusions. He states, however, that the possible occurrence of false or acquired diverticula through stones, tumors, ulcers, and similar causes cannot be disputed.

Until the publication of Bauer's two cases in 1912 no serious clinical or pathological significance was attached to duodenal diverticula. In Bauer's first case there had been signs of pyloric obstruction, and, despite a posterior gastro-enterostomy, the patient died ten days after the operation. The autopsy showed two duodenal diverticula, the larger one of which was about the size of a hen's egg, and situated on the inner pancreatic aspect, involving both the common bile and Wirsung's ducts. Bauer believed that this sac through tension when full caused an insufficiency of the pylorus and a stenosis of the duodenum. In Bauer's second case the duodenal diverticulum was an accidental postmortem discovery. It was filled with a feculent mass, and the duodenum itself was much inflamed and coated with tough, tenacious mucus; the papilla of Vater was inflamed and swollen and closed by a mucous plug. The common bile duct was dilated and the gall-bladder widely distended and filled with stagnant bile. Bauer concluded that in all probability the diverticulum through its feculent contents was the cause of the inflammatory changes in the duodenum and in the bile passages. In two of Wilkie's cases the diverticula were associated with grave disturbances in the adjacent organs, viz., duodenitis and biliary stasis in both cases, while in the first case, there was also an hepatic cirrhosis and in the other an acute hemorrhagic pancreatitis. Wilkie is unwilling, however, to say with certainty that the diverticula were responsible for all the biliary and pancreatic troubles, but thinks there is strong presumptive evidence of an etiological relationship.

[10] Tr. Chicago Pathol. Soc., February, 1913.

In addition to these 4 cases of definite secondary or associated pathological changes reported by others, the radiographic studies of Forssell and Key's case and of my own have unquestionably demonstrated that food and other solid duodenal contents can and at times do enter into these pouches, and remaining there at least four days must undergo fermentation or stagnation, giving rise to very unpleasant local and even far-reaching secondary effects. The marked distention of the second portion of the duodenum and the hypertrophy of its walls in my own case were undoubtedly due to efforts on the part of the gut to force out the contents of the diverticulum. Many of these cases, like Forssell and Key's and the one herewith reported, undoubtedly go on for years with symptoms very suggestive of duodenal ulcer. Now, these cases cannot be diagnosed clinically unless they have real pouch formations which present unmistakable roentgen-ray pictures; frequently, they are so located that ordinary exploratory laparotomy does not reveal them and even at autopsy they may be overlooked unless specially sought for. Is it not therefore possible that a case of clinically suspected duodenal ulcer, reported as not present by the surgeon after operation, may after all at times have been one of these diverticula or even a real ulcer situated not in the usual site, viz., the first portion of the duodenum, but in the second or third portion?

CONCLUSIONS. 1. Duodenal diverticula are of more frequent occurrence than would appear from the number of reported cases.

2. Unless specially sought for they are easily overlooked at operation or autopsy.

3. They can be diagnosed by roentgen-ray examination when they form distinct pouches.

4. They may produce symptoms sufficient to require surgical interference.

5. They can be cured by operation.

THE USE OF RAW EGGS IN PRACTICAL DIETETICS.

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(From the Sheffield Laboratory of Physiological Chemistry in Yale University, New Haven, Conn.)

DURING the past fifteen years evidence has been gradually accumulating which shows that raw egg-white occupies an exceptional position among native protein foodstuffs. Pawlow (1902) observed that this substance has only a feeble ability to stimulate a flow of gastric juice. It acted in this way only as so much water.

Cooked egg-white, on the contrary, calls forth an abundance of juice and unites easily with the hydrochloric acid. On account of the scanty supply of secretion which it induces the raw protein has little opportunity to be digested, but this slender chance is still further diminished by another unusual property. Beaumont (1833), during his famous experiments on Alexis St. Martin, was the first to note that native egg-white left the stomach very rapidly in comparison to other foods, including cooked egg-white itself. Indeed, this substance spent a shorter time in the stomach than any other Beaumont investigated. This observation has more recently been confirmed by Cannon (1904) and by London and Sulima (1905). The former found that the egg-white passed through the pylorus at a rate comparable to that of the carbohydrates, which are among the first foodstuffs to enter the intestine after ingestion. Proteins leave the stomach slowly and egg-white was the only exception noted among those investigated. London and Sulima found that this hasty exit from the stomach was most striking. A few moments after ingestion the egg-white escaped in large gushes through a pyloric fistula. During its stay in the stomach it retains its alkaline reaction and passes into the intestine, for the most part entirely unchanged. After feeding a dog native egg-white these workers recovered large amounts unchanged from a fistula as far down the canal as the ileum.

But even this does not exhaust the means by which raw egg-white escapes gastric digestion, for Abderhalden and Pettibone (1912) and Bizarro (1913) discovered that it offers considerable resistance to the action of pepsin. If, however, the egg-white is coagulated it is more readily acted upon by the pepsin, and proteolysis proceeds further.

We may picture this native protein then as quickly leaving the stomach, accompanied by scanty amounts of gastric juice and little altered by pepsin. This peculiar behavior is consistently carried on in the intestine. Bruno and Klodnizki (1914) and Okada (1915) showed that little or no bile was passed into the intestine after the ingestion of raw egg-white, whereas the same material cooked always caused a good flow of bile.

Once in the intestine the native egg-white continues to oppose the digestive enzymes, for it has remarkably strong antitryptic properties. The trouble is not that trypsin is unable to act upon the protein but that the rate of action is so slow. Bayliss (1908) found that it required seventy hours for the digestion of the raw material to equal that of the cooked, all other conditions being the same in the two cases. Indeed, the trypsin appears not to change the egg-white at all. Vernon (1904) found the antitryptic action to be more marked with this protein than with any other. Hedin (1907), Cohnheim (1912), Abderhalden and Pettibone (1912), Long and Johnson (1913), and Bizarro (1913) have all demonstrated

the strong antitryptic action of egg-white. Not only does it resist digestion itself, but it prevents the digestion of other easily digested proteins, as observed by Delezenne and Pozerski (1903), Vernon (1904), Compel and Henri (1905), and Hedin (1907). This suggests that the true cause of both facts is that the colloidal egg-white absorbs the trypsin, thus cutting down its activity in much the same way as the charcoal in the experiments of Hedin (1906 *b*). Recently it has been shown by Maxwell (1915) that boiled starch absorbs pepsin and so hinders its activity.

In view of both its antipeptic and antitryptic action it is interesting to note that other proteolytic enzymes are also unable to successfully cope with this native protein. Chittenden, Joslin and Meara (1892), and Chittenden (1894) showed that raw egg-white was much more poorly digested than coagulated egg-white by bromelin, the proteolytic enzyme present in the pineapple. Jonescu (1907) and Sachs (1907) found that papain was also practically unable to act upon native egg-white.

Preliminary heating of the egg-white greatly increases its digestibility by trypsin. Talarico (1910) found that there was no effect, however, until the temperature reached 70°, after which there was an orderly liberation of amino-acids up to 130°. Frank (1911) also found cooked egg-white to be better digested than raw, the optimum temperature in his experience being 70° to 75°. Bizarro (1913) considered the best temperature for this preliminary heating to be 80°. Abderhalden and Pettibone (1912) and Long and Johnson (1913) made similar observations.

This brief review of its properties shows that native egg-white offers such obstacles to digestion as to place it in an exceptional position among the proteins. This raises the question as to how the body handles such a substance. Very little upon this point has, up to the present, been recorded, although raw eggs and egg-white have enjoyed a great vogue as the mainstay of various diets, especially for the sick. Steinitz (1898) noted incidentally that raw egg-white caused vomiting and diarrhea in dogs, but this interesting observation remained unnoticed. When the same facts were observed again by Mendel and Lewis (1913) they led to an extended study by the author, carried out during the past year, the details of which have been published elsewhere. This showed native egg-white to be a decidedly indigestible substance. When fed to dogs in any considerable quantity it invariably caused diarrhea and sometimes induced vomiting. The severity of the diarrhea depended largely upon the amount of material ingested, but also, to a less extent, upon the individual susceptibility of the subject. With dogs of 5.5 to 7 kilos in weight four or five egg-whites were sufficient to cause more or less severe diarrhea. Even the whites of two eggs often caused softening of the feces. The stools were abnormal in character, very offensive

in odor, and often contained much mucus. After the ingestion of even small amounts of native egg-white the latter could be recovered unchanged in small quantity from the stools, and when the amount ingested was large the proportion of coagulable protein in the feces was correspondingly increased.

Even when the feces appeared normal undigested egg-white could usually be recovered. In this connection, Tsuchiya's (1908) statement that albumin is never found in normal feces is pertinent.

After eating enough egg-white to give rise to diarrhea the dogs usually lost weight. In a few cases small intestinal hemorrhages were observed. Occasionally samples of urine obtained by catheterization were found to contain small amounts of protein. In all these reactions there was found much variation in the sensitiveness of the subjects, for sometimes a large dog was more easily affected than a small one by the same amount of protein.

It made little difference with the action of the egg-white whether it was eaten alone or mixed with other food. In the latter case the diarrhea was later in appearing. The presence in the food of a substance able to cause a good flow of gastric juice—meat extract for example—had no effect upon the time of appearance or severity of the diarrhea.

It was soon noticed that when the raw protein was fed for several days in succession its ill effects gradually waned. The time necessary for the abatement of the diarrheal action varied from three to five days. If now the ingestion were continued there ensued a period of alternate days of diarrhea and constipation, after which the egg-white ceased to exert any marked action. The tolerance thus developed lasted for a short time even after the feeding of the uncooked material was discontinued. This recalls the tolerance acquired by dogs who receive peritoneal injections of raw egg-white. Cramer (1908), Hamburger (1908), and Oppenheimer (1904) have observed that under such conditions the dogs utilized part of the protein and excreted the rest in the urine. After repeated injections the quantity used rose gradually. It might be supposed that all proteins would appear, at least in part, in the urine after injection intraperitoneally, but Mendel and Lockwood (1904) have shown this not to be the case with edestin and excelsin.

Native egg-white was found poorly utilized. In large doses from 30 to 50 per cent. of that ingested was wasted by being ejected with the feces. After the dogs had grown to tolerate this material it was better utilized, but even in these cases the best figure was about 85 per cent. When Mendel and Lewis (1913) fed this substance to dogs only about half of the nitrogen in the meals appeared in the urine for the following twenty-four hours as contrasted with almost all when meat, casein, and other proteins were fed instead of the egg-white. Steinitz (1898) reported

unchanged egg-white in the feces in considerable quantities. Vogt (1906) and Falta (1906) found that the nitrogen in uncooked egg-white superimposed upon a standard diet was excreted in the urine much more slowly than that ingested in the form of other proteins.

Drying the egg-white at low temperatures did not abate its diarrheal activity nor improve its utilization. Neither did long standing. Falta (1906) also made experiments, using desiccated material, and found in three cases a utilization of 80 per cent., 80 per cent., and 61 per cent. respectively. LeClerc and Cook (1906) found the same substance very poorly utilized.

When dogs ate cooked egg-white in place of the native or desiccated protein they did not have diarrhea and the material was excellently utilized, the utilization being in the neighborhood of 90 per cent. When raw and cooked egg-white were fed on alternate days or periods the differences in the utilization and in the nitrogen balance were striking.

Experiments were made to show at what temperature the change in digestibility became effective. By heating for thirty to forty-five minutes in a double boiler with constant stirring the egg-white suffered little impairment of its activity in causing diarrhea up to 55°. Above this the activity is considerably decreased and disappears entirely at 70°. It should be noted that above 55° coagulation begins and at 70° the protein is entirely coagulated, but is very soft and jelly-like in texture.

In order to show that dogs did not have an exceptional inability to digest native egg-white, experiments similar to the above were made, using rats and rabbits as subjects. These had in both cases the same results. Both rats and rabbits had diarrhea with consequent poor utilization of the protein. The hardy rats, however, were less sensitive than the other animals. That this native protein sustains life in rats poorly in comparison to others is the general conclusion drawn from the work of Falta and Noeggerath (1906), Knapp (1908), Maignon (1912), and Frank and Schittenhelm (1912). Von Knieriem (1885) and Röhmann (1914) reached the same decision from work with mice as subjects. Osborne and Mendel (1911), on the contrary, kept rats growing well on rations containing cooked egg-white as sole protein for as long as one hundred and seventy days. Von Knieriem (1885) found that desiccated egg-white caused rabbits to pass very soft and abnormal feces containing much unchanged egg-white. Mendel and Rose (1911) found it impossible to feed any large quantity of raw egg-white to rabbits without inducing diarrhea.

No other native proteins are known to act in the alimentary tract in the manner brought out by these experiments. On account of the importance of the subject from the stand-point of dietetics it was of interest to determine how raw egg-white

comported itself when ingested by man. The experiments described below lead to the same conclusions already formulated.

The first group of subjects included a number of men and women partaking of a diet consisting largely of raw eggs and milk for the purpose of increasing weight.

Case I.—Subject O. B. This was a man, aged twenty-five years, who took two to three raw eggs beaten up in milk three times a day. During the first three days there was rather severe diarrhea and general malaise and after that regular stools of soft consistency. The subject had previously been somewhat constipated.

Case II.—Subject D. S. was a man, aged forty years, who also took two raw eggs beaten up in milk three times a day. He did not experience diarrhea, but did have regular stools sometimes twice a day, whereas before beginning the diet he had had somewhat obstinate constipation. He drank a large quantity of milk which generally would tend to prevent diarrhea.

Case III.—Subject M. R., a woman, aged twenty-five years, ate six to eight raw eggs per day. The first few days there was extensive diarrhea followed for some time by irregular movements, consisting usually of soft material.

Case IV.—Subject M. H., a young woman, aged twenty-two years, who ate two raw eggs at night and the same number in the morning. There was no decided diarrhea, but previous constipation was overcome and the stools were soft. This subject complained of some intestinal discomfort.

Case V.—Subject D. G., a woman, aged thirty-five years, took two or three raw eggs in milk three times a day. In this case there was diarrhea for two days, although not severe. This was followed by a day without a stool, after which the bowels moved regularly every day. There had been no previous constipation.

Case VI.—A man, aged about thirty-five years, took each night before retiring two raw eggs in whisky. On almost every such occasion he suffered much intestinal discomfort, accompanied with colic-like pains. Considering raw eggs to be "bland" and the whisky beneficial he did not discontinue the treatment for some time.

Another group of subjects ate only the whites of raw eggs experimentally.

Case I.—Subject D. S., a young woman, aged eighteen years, was unaffected by eating the whites of two eggs per day. When the number was doubled, diarrhea ensued accompanied by discomfort and some trouble with intestinal gases.

Case II.—Subject B. B., aged thirty years, remained unaffected by eating every morning the whites of two to four eggs. She did notice discomfort and accumulation of gas. When the number was increased to six per day the subject complained of malaise and took an aversion to the diet. There was flatulence but no diarrhea.

CASE III.—Subject A. B., a child, aged three years. One-half of a raw egg-white ingested each day led to such laxness that the experiment was discontinued after the third day. The diarrhea, then, disappeared at once.

CASE IV.—Subject J. B., aged five years, was, on the contrary, quite unaffected by the same amount of egg-white as was given the last subject.

CASE V.—Subject W. B., a man, aged thirty years, was found quite unsusceptible to the native egg-white, since two to six whites failed to cause any noticeable change in the feces. When half a dozen eggs were eaten at once he experienced decided discomfort, associated with flatulence. An analysis of the stool for nitrogen showed the protein ingested to be only 85 per cent. utilized. Even eight to nine raw whites eaten at one time did no more than soften the feces, but the utilization was still poorer than before, being only 77 per cent. At no time was there any protein in the urine.

CASE VI.—Subject L. M., aged twenty-five years, ate the whites of six raw eggs every third day. On each occasion the stool was soft and unformed.

Falta (1906) found this material to be utilized by man to the extent of 70 per cent. Wolf (1912) reported a still lower value, namely, 50 per cent. In the latter case the feces were of soft consistency although no diarrhea was observed. There was over twice as much nitrogen in the feces when the raw egg was in the diet as when the food contained the same amount of nitrogen in the form of other proteins. On one day there was more nitrogen in the feces than in the urine. The latter did not contain albumin.

Hamburger (1902) and Cramer (1908) claim that albuminuria follows the ingestion of large doses of native egg-white by man. Oertel (1883) had not been able to find albumin in the urine of either dogs or men after the ingestion of large quantities or raw or half-cooked egg-white. Neither did this material cause an increase in excreted albumin in preëxisting albuminuria. Another aspect of this debated problem will be considered later.

It is a matter of common experience that cooked egg-white has not been known to cause any exceptional digestive effects, and is well utilized. Rubner (1879), who seems to be the sole investigator to have fed a subject on cooked eggs only, found the utilization to be 97 per cent. Cathcart and Green (1913) found a delay in the excretion of nitrogen after superimposition of both native and coagulated egg-white, but the delay appears greater in the sulphur than in the nitrogen elimination. These authors and Wolf (1912), who noticed the same facts, believe that the sulphur complexes in the uncoagulated egg-white have power to withstand the digestive enzymes.

Raw egg-white can be made digestible by other means than

heating at 70°. This result can be brought about by incubation with dilute acids and alkalies at 37°; by precipitation with alcohol, chloroform, or ether; by partial digestion with pepsin, and by conversion into alkali metaprotein.

Egg-white is not a homogeneous substance, but consists of at least four components—ovoglobulin, ovalbumin, conalbumin, and ovomucoid. These were separated according to the method of Osborne and Campbell (1900). When fed to dogs the albumin fraction proved to be the indigestible constituent, a result in harmony with the observations of Mendel and Lewis, who found that purified ovalbumin caused profuse diarrhea when fed to dogs. Vernon (1904) states that crystallized albumin is even more resistant to trypsin than native egg-white.

All the experiments so far described were made with egg-white from the egg of the common fowl. That it is not unique in its unusual behavior in the alimentary tract was shown when the egg-white from the egg of the duck was found to act in exactly the same manner.

In contrast to egg-white, egg-yolk was found to be well digested and utilized. There appears to be nothing in the literature to suggest that the latter is indigestible. Mendel and Lewis's (1913) experiments showed the excretion of nitrogen after feeding ovovitellin to be the same as that after meat, a result in opposition to that obtained with both coagulated and uncooked egg-white. In the author's experiments the feeding of egg-yolk either cooked or raw in any quantity of dogs usually caused a rather severe digestive disturbance, of which vomiting was the main symptom. The vomitus contained much bile and sometimes this liquid was alone expelled from the stomach. This suggested that the high fat content of the yolk was the cause of the trouble. This assumption was correct, for when the fat was extracted the residue of crude ovovitellin was eaten by dogs with no untoward effects.

These experiments show, then, that raw egg-white is a decidedly indigestible substance. It may cause diarrhea and vomiting when ingested in any large quantity. Its utilization by the body is poor, since it is used only to the extent of from 50 to 70 per cent. What bearing have these facts upon practical dietetics?

It is difficult to say to what extent raw eggs are ordinarily used. Since there is a wide-spread idea that they are especially digestible and very nutritious, one might expect their use to be common. There is no doubt that this is so when the diet in disease is considered, for raw eggs appear to play an important part in systems of dietetics for the sick. It is likely that Beaumont's (1833) observations gave the first impetus to this dieto-therapeutic movement. According to his views digestion takes place in the stomach and absorption in the intestines. The criterion of digestibility was the time a food remained in the stomach, the assumption

being that it passed the pylorus only when properly prepared by digestion for ensuing absorption through the intestinal mucosa. Since native egg-white left the stomach more rapidly than any other food the conclusion seemed obvious that it is a very readily digested substance. Beaumont says:

"Albumin if taken into the stomach either very slightly or not at all coagulated is perhaps as readily chymified as any article of diet we possess. If coagulated it experiences a very protracted digestion. In the first case the albumin becomes finely coagulated and divided in the stomach."

While the fact that raw egg-white does remain in the stomach only a short time is true, the interpretation of the fact was erroneous. These experiments of Beaumont, the first of their kind, attracted much attention and became widely known. The earlier writers on dietetics based their advice in many details upon his work. Chambers in his *Manual of Diet* (1875), after quoting a table of Beaumont's showing the times spent in the stomach by raw eggs and eggs cooked in various ways, says,

"It may be observed that this is just the order in which they are tasty—that is to say, the degree in which they come with facility into contact with the sensory nerves distributed through the mucous membrane—so that duty and pleasure here, as usually in natural operations, become one."

To such a school nature is always right; it would not be thought possible for her to be so mistaken as to allow albumin to leave the stomach practically undigested.

Although these early views on digestion are no longer supported by such arguments they still appear to be accepted almost unquestioned. In 1906 a Farmers' Bulletin of the United States Department of Agriculture quotes Beaumont's work and helps to spread the impression that raw eggs are very easily digested, since they are "chymified" in one and a half to two hours as against three for soft-boiled eggs. The figures for "artificial digestion," which approximated bodily conditions as closely as possible, are even more impressive, since it appears that it requires eight hours for the digestion of hard-boiled eggs, six hours for soft-boiled eggs, and only four hours for raw eggs. This bulletin, which has been extensively circulated, gives also the results of experiments which show that cooked eggs are thoroughly digested. Still more recently in *Practical Dietetics for Nurses*, Pattee (1910) quotes, "Half subtilized to chyme the liquid food readiest obeys the assimilating powers." Egg-white is then listed as a liquid food and the proper conclusion thus drawn. This notion of the easy assimilation of liquid foods is often mentioned by writers on dietary topics in their discussion of egg-white, and it is taken for granted that such a substance offers little resistance to the digestive juices. How far astray such an assumption may lead one has already been shown.

In the larger and more recent text-books on dietetics the use of raw eggs is generally recommended. Thompson, whose book *Practical Dietetics* is widely used and much quoted, says on this topic:

"Whole raw eggs are very popular in dietetics at present and are often prescribed when a nutritious, highly concentrated food is desired, as in cases of tuberculosis, some forms of anemia, and various wasting diseases; sometimes from eight to ten or twelve are given daily if they can be digested."

Egg albumen is said to be well absorbed and many recipes are given for preparing albumen water in a palatable form. It is stated, without naming Beaumont, that "a raw egg is ordinarily digested in the stomach in one and a half hours, but a baked egg requires from three to four hours."

In *Diet in Health and Disease*, by Friedenwald and Ruhräh (1913), raw eggs are still more strongly recommended. These authors state:

"In various diseases accompanied by loss of flesh and strength, raw eggs in large numbers are prescribed, as many as twenty-four eggs being given in twenty-four hours. Egg albumen is best absorbed when eaten raw. Eggs beaten up in milk are very useful for the diet of the aged when there are diminished powers of digestion. Raw eggs sometimes disagree but this is more often due to faulty preparation than to any real egg idiocyncrasy. In tuberculosis raw eggs are of the greatest value; six to twenty-four whites may be given daily."

These writers—Thompson, Friedenwald and Ruhräh, Pattee, Winthrop (1899) and others—advise raw eggs as part of the diet in the treatment of many diseases, such as typhoid, diphtheria, gastric ulcer, tuberculosis, appendicitis, gastritis, chronic indigestion, etc. We read that "In fevers albumen water helps to supply wasted tissue albumin;" that "Raw eggs in consumption are full of nutrition and very assimilable;" that "Albumen water is utilized by infants, being found very useful in disorders in which some nutritious and easily assimilated food is needed." It is more surprising to find raw egg-white apparently advised in diarrhea and contra-indicated in constipation; to find raw eggs and albumen water prescribed in dysentery, in chronic cases of which "egg albumen and beef juice form the main part of the diet." Again, it is often stated that raw egg-white can be retained or "kept on the stomach" when nothing else can. This is not really true, since it leaves the stomach rapidly, but in a sense contrary to that meant!

In the treatment of typhoid most writers are agreed that indigestible food should not be fed and that "those causing the least intestinal debris" are the best; yet they all unite in advising raw egg-white in the diet. In the current therapy of gastric ulcer albumen water is frequently used, with the object of taking up the

excessive acid. Insofar as it calls forth no more gastric secretion its use may be beneficial, but considering the speed with which it escapes through the pylorus its efficiency in removing acid already present is problematical. One writer says: "The egg-albumen should be prepared in such a manner as to require the least possible expenditure of force in digestion." Cannon (1904) has shown that the intestine expends more motor activity upon the absorption of the carbohydrates than upon that of the fats or proteins. Raw egg-white, however, acts like a carbohydrate in this respect. Another author states that native egg-white is especially valuable for those with a "weak digestion." All the evidence gathered in this paper tends to show that the substance in question requires an exceptionally "strong digestion" if it is to be utilized.

The most whole-hearted advocate of raw eggs appears to be Dr. Ely (1903), who, in "The Fable of the Egg," shows himself a bold practitioner of his own ideas. Again, Beaumont is quoted with nothing to show that anything has been added to the subject in the eighty years since his observations. The number of eggs advised and administered may seem "fabulous," as the author admits. One patient ate 3006 raw eggs in a year while another partook of 5475 in the same time, the latter being "an exemplary subject as to eggs." It is further stated:

"Some moral force is necessary on the part of patient, nurse, and doctor to overcome a repugnance to the treatment. It is to be understood that in every instance they [eggs] have been used for their supporting and restorative influence. Although some patients have died while taking eggs I can think of no case in which death was due to their liberal use. If you give eggs to your patients do not be chicken-hearted in their employment. Do not fear the production of albuminuria from the ingestion of a large amount of egg albumen. Notwithstanding all possible efforts, nausea and vomiting and diarrhea may often be produced and the physician may be thwarted in his object. He will then try the whites of eggs alone. I have given the whites of forty-eight eggs daily for many days to a patient in the critical stages of typhoid fever. Please remember that I am not advocating a fad, specific, or 'cure-all.' I would urge that in some chronic cases of exhausted nerve centers, and in those acute, critical cases that tax resources for maintaining life, they [doctors] should throw away their tonics and possibly stimulants and should gradually lead the stomachs of their patients up to the egg-an-hour practice."

Enough has been quoted, perhaps, to show the reasons hitherto underlying the advocacy of raw eggs. The results of the present study show these reasons to be not well supported and indicate that the use of raw egg-white is decidedly inadvisable. A substance which fails to stimulate a flow of gastric juice and is antipeptic, which hurries from the stomach, calls forth no flow of bile,

and strongly resists the action of trypsin, which is poorly utilized and may cause diarrhea, has evidently little to recommend it as a foodstuff of preference for the sound person, let alone for the invalid. And when the native protein needs only to be coagulated at 70° in order to obviate almost all the effects mentioned, there appears still less reason for using it uncooked. Other considerations strongly support this conclusion. For instance, Stokvis (1864) declared that raw egg-white eaten in quantity is absorbed undigested and excreted in the urine, doing thereby some damage to the renal epithelium. For a number of years this work was disputed by some and confirmed by others. Ascoli (1902) clarified the situation somewhat by stating that the alimentary albuminuria is not generally manifested by sound persons but usually is by the sick. Besides his own observations he cites other investigators who found that small kidney lesions were caused in this way. The amounts of egg used by Ascoli were not unduly large. The work of Hamburger, Oppenheimer, and Oertel on this topic has already been mentioned. It should be stated that the subject is still a debatable one.

It is true that fairly large amounts of raw egg-white need to be ingested for the abnormal digestive effects to be made manifest; but even if small quantities are used, certain disadvantages may follow. The indigestible protein may reach the large intestine and there become a good pabulum for the putrefactive bacteria. Or mixed with other foods it may retard the digestion and lower the utilization of other proteins. Again, it seems more than a coincidence that of all the common proteins egg-white is the most indigestible and at the same time the most common cause of anaphylaxis. According to the latest views on this subject, as stated by Wells (1914), anaphylactic intoxication is caused by the entrance into the blood of intact, foreign protein molecules. If this be so, it would appear that egg-white is a substance peculiarly apt to be the agent in allergy. It leaves the stomach practically unchanged, so that in the intestine it may be absorbed still intact or only slightly altered. The strong antitryptic action it possesses leads to the same danger. Lately, Van Alstyne (1913) has shown that egg-albumen can enter into the circulation unaltered and is excreted in the urine. In order to cause anaphylaxis it appears unnecessary that large amounts should enter the blood, for Wells (1914) has shown that in guinea-pigs sensitivity has been produced with one twenty-millionth of a gram (0.00000005 gm.) of crystallized ovalbumin and fatal results are obtained after sensitization with one millionth of a gram (0.000001 gm.). In fact, small amounts are frequently more effective than large. It may be argued that cleavage products of any protein may be absorbed in small amount. This is true; but Wells has found that the protein molecule loses its anaphylactic properties as soon as it is altered to any extent.

He was not able to get reactions from the proteoses of egg-albumen. Ten Broeck (1914) found that racemized egg-white had no anaphylactic effect either toward itself or toward native egg-albumen. The simpler the protein disintegration products become the less toxic is their action. The thorough gastric proteolysis undergone by practically all proteins except raw egg-white is a potent factor in preventing allergy. It is well established, however, that even cooked egg-white cannot be used by those sensitized. This does not weaken the case against raw egg, for, as already stated, the coagulated egg-white leaves the stomach little less rapidly than the uncooked. In the texts and manuals on dietetics quoted above the advice to use raw or even cooked eggs is frequently safeguarded by the caution that certain people are peculiarly susceptible to this foodstuff, and it would appear from the cases cited in professional journals that such sensitiveness is not uncommon. Schloss (1913) reported an interesting case in which the feeding of raw egg-white to a child ten days old caused it to react for years to either cooked or uncooked egg-albumen. The sensitizing substance appeared to be ovomucoid while ovalbumin seemed to be inactive.

With the improved technic for rectal feeding effected by the drip method there has come an increased interest in this kind of alimentation. Since the foods used must be liquid it is natural that raw egg-white should suggest itself for the protein requirements. As early as 1869, Voit and Bauer, however, concluded that this foodstuff was practically worthless for the purposes, a conclusion also reached by Eichorst. Previously it had been stated that salt aided in the absorption of the egg-white, but Eichorst doubted this and stated that the salt caused diarrhea. Czerny and Latschenberger (1874) and Ewald (1887) also found the salt to be of no value. More recent studies of rectal alimentation tend to show that the amount of protein which can be utilized in this way is unimportant compared to the requirements of the body, a conclusion supported by the work of Adler (1915). Furthermore, it is considered doubtful if unaltered proteins can be absorbed from the colon (Pfeiffer, 1906). If this is so, native egg-white must be considered an especially poor substance for nutrient enemas in view of its pronounced antitryptic properties.

It must not be assumed from the foregoing discussion that native egg-white is considered a toxic or otherwise dangerous substance. But the evidence regarding its behavior in the alimentary canal is taken to show that no advantage accrues to the body by using it raw rather than cooked. Furthermore, when the diet of those seriously ill is considered it may fairly be asked in the light of scientific evidence if the current extensive use of raw eggs is not illogical and inadvisable?

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THE TREATMENT OF BRONCHIAL ASTHMA BY VACCINATION, WITH REPORT OF CASES.

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Until recently Osler has described asthma as "so imperfectly understood that it is impossible to give a satisfactory definition." The pathology included spasm of the bronchi and spasm of the respiratory muscles and diaphragm and vasomotor disturbances of the bronchial mucous membrane. Etiology included heredity, a neurotic basis, and in addition other factors, such as nasal obstruction by polypi and hypertrophied turbinates, climatic effects, and gout.

Measures for cure generally proved useless; to help the individual attacks, adrenalin, morphin, strychnin, atropin, potassium iodide, lobelia, stramonium, and asthma powders have all been extensively used, but no means of preventing future attacks has been found.

Although we must admit that asthma is still imperfectly understood and that its etiology is not always clear, yet the past few years have added much information which will without doubt be a clue to the eventual relief of this harassing malady.

When a foreign proteid is injected in minute quantities into the animal body, sensitization occurs; the injection of a large amount of the same proteid[1] after a certain interval of time (usually twenty-one days) results in a set of symptoms characterized by sneezing, labored breathing, skin eruptions, joint and glandular swellings, edema, and cardiac palpitation; if the attack be severe enough, convulsions and death follow; this reaction is called anaphylaxis. Anaphylaxis implies a hypersensibility; either a natural one exemplified by an attack of hay fever or serum sickness, or an artificial one brought about for example by a previous injection of horse serum.

Animal experimentation[2] has taught us that when the foreign proteid is injected into the body in proper amounts, specific antibodies or amboceptors are produced for this proteid; if after certain periods of time the injections be repeated in constantly increasing quantities, some of these antibodies in the presence of compliment and antigen, are protective; this holds true whether the invading substance be introduced subcutaneously, intravenously, intraperitoneally or by mouth. The foreign proteid contains two sub-

[1] Rosenau and Anderson: Hygienic Laboratories Bulletin, 1908, Nos. 29 and 45.
[2] Zinsser, H.: Anaphylactic Phenomena. Harvey Lectures, 1914–1915, series No. 10.

stances, one toxic which may cause death, and one which immunizes the individual.[3]

Immunization is obtained by introducing this foreign proteid into the system in small quantities frequently repeated and in increasing doses, within seven or eight days each, during the pre-anaphylactic or anti-anaphylactic period; if the period be too long the hypersensitive state may lead to serious or fatal consequences; this hypersensitive state may be transmitted from mother to offspring.

Bacterial anaphylaxis is not so readily produced as that by foreign albumens, as egg and serum albumens.

Food protein is absorbed as amino-acids and then reconverted into protein in the proper form for utilization; if by any chance it undergoes incomplete breaking down, and some of the by-products are absorbed, sensitization occurs; if after a certain time (ten to fourteen days) the same article is again eaten, anaphylaxis results in the form of asthma, urticaria, or erythema (the so-called indigestion rash). This same sequence probably occurs in the case of injected proteids, whether horse serum, bacteria, or pollen; if not converted into a proper and available form for use, their by-products sensitize the individual so that a second dose is anaphylactic.

Asthma is undoubtedly in some cases an expression of anaphylaxis; clinically it resembles the hypersusceptibility produced in animals by the injection of foreign proteid. Patients with this disease become sensitized to some form of proteid by absorption from the nasal mucus membrane, alimentary canal, or from some focus of infection, and react with an attack of bronchial asthma upon an intoxicating dose of the poison (Meltzer). Babcock recalls the case of a sufferer from asthma who was operated upon for gall-stones, with relief of the asthma, and as long as drainage of the gall-bladder was maintained there was no asthma, but with stoppage of drainage it returned; finally, with cure of the gall-bladder the asthma disappeared. Likewise the removal of nasal polyps restores drainage to the accessory sinuses of the nose and relieves a pent-up focus of absorption which has been causing attacks; the removal of hypertrophied turbinates acts in the same way. In some cases the smell of horses or of the stable in a sensitized individual will bring on an attack. Sometimes the injection of horse serum even in the form of antitoxin will produce an attack;[4] a friend of mine who received a small immunizing dose of diphtheria antitoxin had such a severe anaphylactic reaction with asthma that his life was despaired of. Asthmatic attacks occurring with hay fever, and due to the pollen of rag weed, golden rod,[5] etc., are of the same origin; inoculation with constantly increasing emulsions

[3] Vaughan, V. C.: Proteid Split Products in Immunity and Disease.

[4] Sturtevant, Mills: Serum Sickness in a Series of 500 Patients Treated with Diphtheria Antitoxin, Arch. Int. Med., vol. xvii, No. 1.

[5] Gottlieb and Oppenheimer: Active Immunization in Hay Fever, Biochemical Bull., New York, 1915, No. 4, p. 127.

of these pollens, or polyvalent emulsions, will cure or improve the attacks. Egg proteid also causes attacks in some individuals. I have in mind a child who had asthmatic attacks after eating eggs, and which attacks cleared up after a change in diet. The urticaria following the ingestion of fish is of the same character; likewise the urticaria following the injection of antitoxin.

Another source of attack (and one with which I have been working) is due to the presence of bacteria, primarily Streptococcus viridans or Streptococcus hemolyticus, secondarily Micrococcus catarrhalis.[6] These cases are obviously infective, and the more asthma I see the larger I think this group is; they occur with bronchitis, and sometimes run an acute course with febrile reaction, increase in pulse rate, cough, and sputum, and are often followed by emphysema.

If the sputum be collected in a sterile cup or Petri dish, washed, and a loop stirred in blood agar and poured in a Petri dish, and later streaked on North's medium, streptococcus can practically always be grown. Whatever the variety of germ, whether Streptococcus viridans or Streptococcus hemolyticus, an autogenous vaccine will cure the attacks. It is best given twice a week, in constantly increasing strength, for twelve to twenty injections. It is much better to give such dosage that local reaction occurs, although I have had cures in patients who showed no local reaction. On the other hand I have had cases which showed no improvement until doses were given in sufficient quantity to cause local reaction. I have adopted the practice of beginning with 100,000,000 in adults and feeling my way cautiously until finding the dose that caused local reaction, and then provoking a local reaction on every injection. If at any time the local reaction be too severe, or if general symptoms occur in the form of fever, chilliness, general malaise or aches, or increase in the asthma, I allow a rest for a period before beginning again, using my judgment as to continuing the same dosage or dropping back to a smaller one; it is better to avoid going backward if possible. 1000 million is often far enough to carry them, although more obstinate cases may require 2000 million, and I have carried them to 3000 million and higher. It is very striking to see the asthma clear up after the first injection, as has happened in a number of my cases. The longest period of cure I have to report is two years. I have been struck with the fact that streptococcus seems to be the chief offender; one case which had very foul sputum, and who showed Bacillus Friedländer, had to leave town, so that I had no opportunity of vaccinating him. I have had no pneumococcus cases. Micrococcus catarrhalis, I am convinced, is usually a mouth infection in asthma. I do not find it often in sputum that is carefully washed, and when the specimen for culture is carefully selected. Vaccination by catarrhalis seems to have had very little action on the asthmatic attacks when mixed infection

[6] Allen, R. W.: Vaccine Therapy and Opsonic Treatment.

is present. Babcock reports excellent results in a case of mixed infection, in which he used a mixed vaccine of pneumococcus, streptococcus and an anaërobic bacillus.[7] After inoculation for a time at semiweekly intervals it is usually advisable to make the intervals weekly.

In analyzing the following cases several facts are striking.

1. Clearing up of the asthma after the first or second injection (Cases 2, 3, 4, 6, 12, 14).

2. Cases that progressively improved from the time vaccines were started (Cases 1, 9, 14, 15).

3. Cases that did well but had occasional short relapses (Case 5, much improved, but could not continue treatment); case 10.

4. Obstinate cases which were finally cured (case 7) or improved (case 8).

5. Unimproved, case 11 (tuberculosis).

6. Of the 16 cases, 12 were cured, 3 were improved, and only 1 unimproved (tuberculosis).

7. Twelve cases required from 9 to 16 injections, extending over a period of from four to eleven weeks. Two cases were given treatments of fifteen and seventeen weeks respectively.

I should advise always using the regular vaccine or tuberculin syringe divided into hundredths, as no accurate count can be made with the ordinary hypodermic syringe, especially when small volumes are given. The following cases will show the preparation and method of administration of the vaccine, and the result of treatment:

Case I.—L. B. R., aged six years. December 18, 1914. The child has had various attacks of bronchitis associated with asthma since nine months of age; attacks coming on at intervals of a few weeks and lasting from two to four days, accompanied by cough, dyspnea, temperature, sleepless nights, and loss of weight; they were harassing to the child and a cause of much anxiety on the part of the parents. As treatment had but slight and temporary effect, a swab was made from the larynx during an attack, and Gram-positive cocci obtained, which were arranged in long chains; on blood agar these colonies were each surrounded by an area of hemolysis. Vaccines were prepared and administered as follows:

Dec. 18.	Streptococcus hemolytic	5,000,000.	No reaction.		
23.	" "	10,000,000.	Temperature	100.6	
30.	" "	25,000,000.	"	100.4	improved.
Jan. 6.	" "	50,000,000.	"	100.6	"
13.	" "	75,000,000.	"	100.0	"
20.	" "	100,000,000.	"	100.0	"
28.	" "	125,000,000.	"	100.0	"
Feb. 5.	" "	150,000,000.	"	100.0	cured.
10.	" "	175,000,000.	"	100.4	"
19.	" "	200,000,000.	"	100.6	"
24.	" "	250,000,000.	"	100.4	"
Mar. 3.	" "	300,000,000.	"	100.4	"
9.	" "	350,000,000.	"	100.4	"

Cured; at the present writing (February, 1916) the child has had no further attacks, and is perfectly well.

[7] Journal of the American Medical Association, vol. lxiv, No. 26.

December, 1916. This patient has relapsed and is again under treatment.

CASE II.—Charles Spanze, aged twenty-five years; Italian; fruit vendor February 15, 1915.

No alcoholic nor venereal history. For four months has had attacks of asthma, every three or four weeks, lasting two or three days each and interfering with sleep. He had two hemoptyses three months ago, has lost seven pounds, and has had a few night sweats. Physical examination reveals no positive signs of tuberculosis, but chest is filled with squeaking rales and gives the signs of emphysema. Sputum examination shows no tubercle bacilli; Gram stain shows positive cocci in the washed sputum, and poured sputum reveals Streptococcus viridans in blood agar; vaccines were made from this and administered as follows:

Feb. 15.	Streptococcus viridans.	50,000,000.	Slight local reaction.	No asthma after this first injection.
18.	" "	100,000,000.	Slight local reaction.	
21.	" "	300,000,000.	" " "	
24.	" "	500,000,000.	" " "	
27.	" "	600,000,000.	" " "	
Mar. 3.	" "	700,000,000.	" " "	
6.	" "	800,000,000.	" " "	
9.	" "	900,000,000.	" " "	
12.	" "	1,000,000,000.	" " "	

On March 12 he was discharged cured, having gained four pounds. A letter from him five months later stated he had had no return of his asthma.

On October 5, seven months after discharge, he was back complaining of cough, slight difficulty in breathing, but no distinct asthma. Sputum was again examined; showed no tubercle bacilli; Gram-negative cocci, in pure culture, vaccines were again made and administered.

Oct. 22.	Micrococcus catarrhalis.	100,000,000.	Slight local reaction.
25.	" "	200,000,000.	" " "
29.	" "	300,000,000.	" " "
Nov. 2.	" "	400,000,000.	" " "
5.	" "	600,000,000.	" " "
9.	" "	800,000,000.	" " "

During these three weeks his attacks became more frequent and of greater severity, so that 500 million streptococci were added to the vaccine with the result of a severe local reaction, chilliness, and temperature 102°, but with a cessation of the asthma. Sputum was again ordered and cultured, when pure Streptococcus viridans were grown on blood agar, and vaccines prepared.

Nov. 12.	Micrococcus catarrhalis.	1,000,000,000.	Intense local and general reactions; temperature 102°, chilliness; severe local reaction; no more asthma.
	Streptococcus viridans.	500,000,000.	
16.	Micrococcus catarrhalis.	1,200,000,000.	
	Streptococcus viridans.	700,000,000.	
23.	Micrococcus catarrhalis.	1,300,000,000.	Injections at weekly intervals. No asthma; marked local reactions.
	Streptococcus viridans.	700,000,000.	

No more catarrhalis were given, as they seemed to do no good when patient was getting them alone.

30.	Streptococcus viridans.	700,000,000.	No asthma; marked local reaction.
Dec. 7.	" "	800,000,000.	" " " " " "
14.	" "	1,000,000,000.	" " " " " "
21.	" "	2,000,000,000.	By mistake. " " "
Jan. 11.	" "	2,250,000,000.	No asthma; " " "
18.	" "	2,250,000,000.	" " " " " "
25.	" "	2,200,000,000.	" " " " " "

Discharged cured; has gained three pounds more. An urticarial eruption followed the last injection. Had he been put on viridans at the beginning instead of catarrhalis, I doubt if he would have had any return. One month later he had gained four pounds more, a gain of fifteen pounds since starting treatment and he felt perfectly well.

CASE III.—L. Wilson, aged thirty-three years, conductor. April 1, 1915.

His mother has had asthma for forty years. He has no alcoholic nor venereal history.

His first attack of asthma was two months ago, lasting thirty hours, after which it disappeared for five weeks; since that time it has been fairly continuous, with choking and coughing in the morning and difficult breathing at night; the cough has been very harassing.

Physical examination shows an overacting heart, 104. Lungs give slight comparative dulness at the right apex, with slightly prolonged and high-pitched expiration; there are sibilant rales over all. Weight, 125 pounds.

Sputum shows many Gram-positive cocci, some in clumps and some in chains. No tubercle bacilli; sputum poured in blood agar gives Streptococcus viridans. Vaccines were given as follows:

Apr. 15.	Streptococcus viridans.	50,000,000.	Slight reaction.	
18.	" "	100,000,000.	" "	
21.	" "	200,000,000.	Moderate "	
24.	" "	300,000,000.	" "	
27.	" "	500,000,000.	" "	
30.	" "	700,000,000.	" "	
May 3.	" "	800,000,000.	" "	There was no return of the asthma after the first injection.
6.	" "	900,000,000.	" "	
9.	" "	1,000,000,000.	" "	

Discharged cured May 9, "feeling better than for the past two years;" weight 131 pounds, a gain of 13 pounds. In August of the same year he reported no return, and in February of the following year he reported continued cure.

CASE IV.—Celia Jaffe, aged twenty-eight years, October 22, 1915.

This patient had attacks of asthma in childhood until fourteen years of age. It returned seven months ago at intervals of three or four days, lasting one or two nights each time. Cough only recently; no hemoptyses; no sweats; no loss of weight.

Physical examination shows a well-nourished woman, breathing labored, with scattered sibilant and sonorous rales.

Sputum shows many Gram-positive cocci, no tubercle bacilli. Blood agar shows Streptococcus viridans.

Oct. 30.	Streptococcus viridans.	200,000,000.	No local reaction.	
Nov. 4.	" "	400,000,000.	" " "	No asthma.
7.	" "	600,000,000.	" " " " "	
10.	" "	800,000,000.	" " " " "	
13.	" "	1,000,000,000.	Good " " " "	
16.	" "	1,100,000,000.	" " " " "	
20.	" "	1,300,000,000.	" " " " "	
24.	" "	1,300,000,000.	" " " " "	
27.	" "	1,300,000,000.	Several local and general reaction so none was given for two weeks.	
Dec. 11.	" "	1,300,000,000.		
21.	" "	1,500,000,000.	No asthma; severe itching of the skin, but nothing to be seen.	

Discharged cured December 21.

Case V.—James Burk, aged twenty-five years; sailor. November 5, 1915.

Not alcoholic. Eighteen months ago had cough and pain in the chest; mucopurulent sputum; could not work for three weeks; cough and sputum were worse in the morning; he lost 35 pounds, but is now gaining. While at sea he is well, but on shore his breathing is affected by bad weather, and he has wheezing and dyspnea.

Physical examination shows a well-built and well-nourished man, with hyper-resonant chest and with sibilant and sonorous rales; no localized signs.

Sputum shows Gram-positive and Gram-negative cocci; blood agar, Streptococcus viridans; no tubercle bacilli. Vaccines were given as follows:

Nov. 10	Streptococcus viridans.	100,000,000.	No reaction; no asthma.
13.	" "	200,000,000.	" " " "
16.	" "	300,000,000.	" " " "
20.	" "	500,000,000.	" " slight oppression.
23.	" "	800,000,000.	" "
27.	" "	1,200,000,000.	Severe attack with advent of severe easterly storm; no return of asthma. As he had to go to sea he was now discharged improved, "by his own statement feeling very much better;" the severe attack with the advent of the easterly storm was the only attack after injections were started.
30.	" "	1,500,000,000.	
Dec. 3.			

Case VI.—Meyer Grisham, aged twelve years, school. November 10, 1915.

For some months has had attacks at night, so that he had to sit up out of bed to breathe; attacks were at intervals of a few days.

Physical examination negative except for asthma.

Culture showed Gram-positive and Gram-negative cocci. Streptococcus viridans on blood agar. No tubercle bacilli. Vaccines as follows.

Nov. 13.	Streptococcus viridans.	100,000,000.	Severe local reaction.
	Micrococcus catarrhalis.	100,000,000.	
16.	Streptococcus viridans.	200,000,000.	" " " no asthma.
	Micrococcus catarrhalis.	200,000,000.	
20.	Streptococcus viridans.	300,000,000.	" " " " "
	Micrococcus catarrhalis.	300,000,000.	
27.	Streptococcus viridans.	400,000,000.	Moderate " " " "
30.	" "	500,000,000.	" " " " "
Dec. 3.	" "	600,000,000.	" " " " "
7.	" "	700,000,000.	Good " " " "
18.	" "	700,000,000.	Slight; weekly injections now.
21.	" "	800,000,000.	Good local reaction.
28.	" "	1,000,000,000.	

Discharged, December 28, cured; no attacks since treatment was begun.

Case VII.—Emma Wilson, aged sixty years; dressmaker. November 30, 1915.

Father died of tuberculosis; patient has one son who had asthma and who was cured by inoculation (see Case III). At the age of eighteen years patient had asthma and hay fever, which attacks

recurred every year; twenty years ago she moved from the country to New York City, when the hay fever disappeared but the asthma continued, and increased to such an extent that attacks were at intervals of a few days. Upon returning to the country in the summer the hay fever would return. Asthma, however, has been nearly continuous for years.

Physical examination shows a well-nourished woman with scattered sibilant and sonorous rales and labored breathing.

Sputum gave no tubercle bacilli, but Gram-positive cocci in clumps, the isolated ones being in chains. On blood agar, streptococcus grew in pure cultures. Vaccines were given as follows:

Nov. 30.	Streptococcus viridans.	100,000,000.	No reaction; no improvement.
Dec. 4.	" "	300,000,000.	No reaction; bad asthma with storm.
7.	" "	500,000,000.	Slight reaction; improved, slight asthma.
11.	" "	750,000,000.	Slight reaction; still has asthma.
14.	" "	1,000,000,000.	Moderate reaction; improvement after this.
21.	Seven days.	1,250,000,000.	" " one attack since last.
28.	Seven "	1,500,000,000.	" " oppression but no real asthma.
Jan. 8.	Eleven "	1,500,000,000.	Moderate reaction; no asthma, feels better.
25.	Seventeen "	1,500,000,000.	" " well until two days ago, slight attack.
Feb. 1.	" "	1,500,000,000.	Moderate reaction; no asthma.
5.	" "	1,600,000,000.	" " " "
12.	" "	2,000,000,000.	" " " "
16.	" "	2,250,000,000.	" " " "
23.	" "	2,500,000,000.	" " " "

Discharged, cured, February 23.

This was a case of many years' standing and proved obstinate. Patient was irregular in her attendance, but after improvement began it was continuous, and was followed by complete cure.

Case VIII.—Nita Connolly, aged twenty-five years; colored; domestic. For two years has had attacks at biweekly intervals, oppressed breathing, with cough and expectoration.

Physical examination negative except for asthmatic breathing.

Sputum showed no tubercle bacilli; Gram-positive cocci which proved to be Streptococcus viridans on blood agar. Vaccines were given as follows:

Nov. 27.	Streptococcus viridans.	100,000,000.	Not autogenous.
Dec. 11.	" "	100,000,000.	" " improved.
21.	" "	250,000,000.	Autogenous; "
Jan. 3.	" "	300,000,000.	Good reaction.
8.	" "	500,000,000.	Good reaction; one attack.
15.	By mistake.	2,700,000,000.	Marked reaction; local and general; no asthma.
22.	"	1,700,000,000.	Marked reaction; no asthma.
Feb. 5.	"	1,700,000,000.	Moderate reaction; mild attack with grippe.
11.	"	2,000,000,000.	Not autogenous; no asthma.
15.	"	2,000,000,000.	No asthma.
22.	"	2,500,000,000.	No asthma.

This girl was irregular in attendance and obstinate in reaction, but was greatly improved.

Case IX.—Charles Clement, aged eight years, November 25, 1915. Cough and colds for one year; indisposition to play; no loss of weight; no hemoptyses; no sweats; never well. One year ago was seen by Dr. F. L. Keays, who diagnosed bronchopneumonia; but

the signs of this cleared up. The child, however, has remained listless and half sick. Various consultations have been held upon him, with the result that no positive diagnosis of tuberculosis could be made, and no tubercle bacilli have been found in the sputum after repeated examinations. Recently he has complained of pain in the back, and examination revealed a dorsal kyphosis, with spasm and pain upon motion. Asthma has existed over the entire period, which greatly harasses him and interferes with sleep. I saw him in consultation December 1, and on examination he revealed the dorsal kyphosis and well-defined signs of cavity in his left upper lobe. I took this to be a bronchiectatic cavity following his bronchopneumonia. Sputum examination showed no tubercle bacilli, but a culture of Streptococcus viridans and Staphylococcus albus. I made a vaccine of this and sent it to Dr. Keays, who administered it as follows:

Dec.	5.	Streptococcus viridans.	35,000,000.	No reaction; no result.
		Staphylococcus albus.	35,000,000.	
	8.	Streptococcus viridans.	70,000,000.	
		Staphylococcus albus.	70,000,000.	" " " "
	12.	Streptococcus viridans.	140,000,000.	
		Staphylococcus albus.	140,000,000.	" " " "
	16.	Streptococcus viridans.	280,000,000.	
		Staphylococcus albus.	280,000,000.	Sleeps better; less asthma.
	19.	Streptococcus viridans.	560,000,000.	
		Staphylococcus albus.	560,000,000.	
	23.	Streptococcus viridans.	800,000,000.	Improved.
	26.	" "	1,200,000,000.	"
	30.	" "	1,500,000,000.	" slight local reaction.
Jan.	2.	" "	1,500,000,000.	" " " "
	6.	" "	1,500,000,000.	" " " "
	9.	" "	1,500,000,000.	" " " "
	13.	" "	1,500,000,000.	No asthma; sleeps well.
	16.	" "	1,800,000,000.	" " " "
	20.	" "	1,800,000,000.	" " " "
	27.	" "	1,800,000,000.	
Feb.	3.	" "	2,000,000,000.	

Entirely cured of asthma, sleeps all night and is very much more comfortable; of course he has his original condition, and Dr. Keays is inclined to think he has sarcoma of the lung. This boy was a very unpromising case, and I hesitated to undertake his cure, but he did remarkably well. I heard from him two months later, and he was still free from asthma.

CASE X.—J. S., aged twenty-one years. January 20, 1916.

Various attacks for a period of one year, coming on at intervals of two or three weeks at first, but latterly they have been continuous.

Physical examination shows only labored breathing, with whistling rales. Sputum shows no tubercle bacilli, but Streptococcus viridans and Micrococcus catarrhalis. Vaccines were given as follows:

Feb.	1.	Streptococcus viridans.	210,000,000.	Improved; no reaction.
	5.	" "	300,000,000.	" less cough.
	8.	" "	400,000,000.	" local reaction.
	12.	" "	800,000,000.	" marked local.
	15.	" "	1,000,000,000.	Bad attack with very cold weather.
	19.	" "	1,250,000,000.	Much better.
	24.	" "	2,250,000,000.	No asthma; moderate reaction.
Mar.	2.	" "	2,500,000,000.	" " " "

This boy reported great improvement. As he thought himself well he stopped coming, and I feel sure has had no return.

CASE XI.—Nellie B., aged thirty years; housewife. November 30, 1915.

For years had cough; dyspnea; smothering, especially at night. During last pregnancy the attacks cleared up six months before confinement and appeared three weeks after.

Physical examination shows a pale thin woman whose lungs are filled with sibilant and sonorous rales; at the right apex are slight dulness and subcrepitant rales. Sputum shows no tubercle bacilli, but Streptococcus viridans in blood agar.

This woman was vaccinated for two months twice a week, and carried as high as 3100 million without the slightest benefit. She stopped coming of her own accord, so I had no chance of increasing the doses further.

The following cases are loaned me through the courtesy of Dr. T. W. Hastings.

CASE XII.—Miss B. G. T., aged 41 years. June 13, 1914.

Had hay fever for fourteen years; asthmatic attacks, including horse asthma, with cough and expectoration. She was in Saranac in 1914, with supposed tuberculosis. Culture now made of the sputum, and Streptococcus viridans and Micrococcus albus isolated. Vaccines were given as follows:

Aug. 20.	{Streptococcus viridans.	120,000,000.	Worse for three days following.
	{Micrococcus albus.	60,000,000.	
25.	" "	240,000,000.	No asthma.
	" "	120,000,000.	
Sept. 1.	" "	360,000,000.	Slight local reaction.
	" "	180,000,000.	
8.	" "	480,000,000.	No asthma.
	" "	240,000,000.	
24.	" "	600,000,000.	"
	" "	300,000,000.	
Oct. 7.	" "	720,000,000.	"
	" "	360,000,000.	
18.	" "	840,000,000.	"
	" "	420,000,000.	
Nov. 1.	" "	960,000,000.	"
	" "	480,000,000.	
10.	" "	1,200,000,000.	"
	" "	600,000,000.	

Discharged, cured, November 10. No attacks after the second injection.

CASE XIII.—Miss E. U., aged eighteen years; school. April 15, 1910.

For years had cough and wheezy breathing and real asthmatic attacks, especially at night; sputum culture showed Streptococcus and Micrococcus catarrhalis. Vaccines were given as follows:

Apr. 30.	{Streptococcus pyogenes.	66,000,000.	Mild local reaction.
	{Micrococcus catarrhalis.	60,000,000.	No reaction; no asthma.
May 10.	" "	132,000,000.	No asthma.
	" "	132,000,000.	
18.	" "	165,000,000.	" "
	" "	165,000,000.	
26.	" "	165,000,000.	" "
	" "	165,000,000.	
31.	" "	225,000,000.	Moderate local reaction.
	" "	225,000,000.	No asthma.
Jan. 4.	" "	225,000,000.	" "
	" "	225,000,000.	
10.	" "	330,000,000.	" "
	" "	330,000,000.	

Discharged, cured, January 10. No attacks since treatment started.

Case XIV.—Mrs. O. H. February 11, 1915.

A sufferer from asthma for years; no tuberculous element present. Sputum showed Gram-positive and negative cocci; no tubercle bacilli present. Vaccines were administered as follows:

Mar. 18.	{Streptococcus viridans.	100,000,000.	
	{Micrococcus catarrhalis.	50,000,000.	
22.	" "	200,000,000.	
	" "	100,000,000.	
26.	" "	300,000,000.	
	" "	150,000,000.	
30.	" "	400,000,000.	No local but slight local reaction.
	" "	200,000,000.	
Apr. 3.	" "	500,000,000.	" " " " "
	" "	250,000,000.	
7.	" "	600,000,000.	" " " " "
	" "	300,000,000.	
11.	" "	700,000,000.	" " " " "
	" "	350,000,000.	
15.	" "	800,000,000.	" " " " "
	" "	400,000,000.	
19.	" "	900,000,000.	" " " " "
	" "	450,000,000.	
23.	" "	1,000,000,000.	Slight local; no asthma.
	" "	500,000,000.	
28.	" "	800,000,000.	" " "
	" "	400,000,000.	
May 2.	{Streptococcus viridans.	1,000,000,000.	
	{Micrococcus catarrhalis.	500,000,000.	
6.	" "	1,200,000,000.	Severe local reaction.
	" "	600,000,000.	
10.	" "	1,400,000,000.	" " "
	" "	700,000,000.	
17.	" "	1,600,000,000.	" " "
	" "	800,000,000.	
24.	" "	1,800,000,000.	Marked " "
	" "	900,000,000.	
June 1.	" "	1,800,000,000.	" " "
	" "	900,000,000.	
8.	" "	2,000,000,000.	Slight " "
	" "	1,000,000,000.	
15.	" "	2,200,000,000.	
	" "	1,100,000,000.	
22.	" "	1,600,000,000.	
	" "	800,000,000.	
30.	" "	2,000,000,000.	
	" "	1,000,000,000.	
July 8.	" "	2,400,000,000.	
	" "	1,200,000,000.	
16.	" "	2,800,000,000.	
	" "	1,400,000,000.	
23.	" "	3,200,000,000.	
	" "	1,600,000,000.	
30.	" "	3,600,000,000.	
	" "	1,800,000,000.	
Aug. 6.	" "	4,000,000,000.	
	" "	2,000,000,000.	
13.	" "	4,400,000,000.	
	" "	2,200,000,000.	
20.	" "	4,800,000,000.	
	" "	2,400,000,000.	
27.	" "	5,200,000,000.	
	" "	2,600,000,000.	

There was only one attack of asthma since beginning treatment. Injections were followed within a few hours by very mild attacks, but were of no consequence and of only focal character. She reports great improvement and feels better than she has felt for years. Cured.

Case XV.—Lieut. B., U. S. A., aged twenty-nine years. January, 1910.

Ever since childhood has had attacks of bronchitis and asthma. In 1907 he had an operation on his turbinates, with vaccines, and was cured. For the past two weeks he has had shortness of breath

at night, but no true asthma. Physical examination shows sibilant and sonorous breathing, but no local signs. Sputum was cultured and vaccines made of equal parts of Streptococcus hemolyticus and Micrococcus catarrhalis.

Jan.	14.	Streptococcus hemolyticus and Micrococcus catarrhalis.			27,000,000	each.
	18.	"	"	"	54,000,000	"
	21.	"	"	"	81,000,000	"
	25.	"	"	"	108,000,000	"
	28.	"	"	"	135,000,000	"
Feb.	1.	"	"	"	162,000,000	"
	8.	"	"	"	198,000,000	"
	15.	"	"	"	216,000,000	" weekly intervals.
	25.	"	"	"	243,000,000	each ten day intervals.
Mar.	7.	"	"	"	270,000,000	each.

The following case does not belong strictly to this class, but I enter it as a matter of interest as belonging to a spasmodic group like asthma.

CASE XVI.—P. L. C., aged eleven years; school. October 30, 1914.

Has always been subject to attacks of coryza and sore throat accompanied by spasmodic laryngitis. Tonsillectomy five years ago with only moderate results. He lost fifty-five days' schooling the past year, owing to frequent colds. Recently had a severe coryza and bronchitis, with spasmodic cough. Physical examination was negative. Sputum cultured. Streptococcus viridans and Micrococcus albus grown; no tubercle bacilli found. Vaccines were given as follows:

Nov.	23.	Streptococcus viridans.		25,000,000.	
		Micrococcus catarrhalis.		10,000,000.	
Dec.	2.	"	"	37,000,000.	Local for twenty-four hours.
		"	"	15,000,000.	
	14.	"	"	50,000,000.	
		"	"	20,000,000.	
	18.	"	"	62,000,000.	
		"	"	25,000,000.	
	21.	"	"	75,000,000.	
		"	"	30,000,000.	
Jan.	4.	"	"	100,000,000.	
		"	"	40,000,000.	
	8.	"	"	125,000,000.	
		"	"	50,000,000.	
	11.	"	"	150,000,000.	No reaction.
		"	"	60,000,000.	
	18.	"	"	250,000,000.	
		"	"	100,000,000.	
	22.	"	"	300,000,000.	
		"	"	150,000,000.	
	27.	"	"	350,000,000.	
		"	"	175,000,000.	
Feb.	1.	"	"	400,000,000.	
		"	"	200,000,000.	
	8.	"	"	400,000,000.	
		"	"	200,000,000.	
	15.	"	"	400,000,000.	Coryza for two weeks; no reaction.
		"	"	200,000,000.	
Mar.	1.	"	"	400,000,000.	
		"	"	200,000,000.	
	8.	"	"	450,000,000.	
		"	"	225,000,000.	
	18.	"	"	500,000,000.	
		"	"	250,000,000.	

Bronchitis much improved; there has been no return of the spasmodic laryngitis.

I wish to express my thanks to Dr. T. W. Hastings, for his kind assistance, also to Dr. W. C. Thro for many valuable suggestions.

THE EFFECT OF ANESTHESIA AND OPERATION ON KIDNEY FUNCTION AS SHOWN BY THE PHENOLSULPHONEPHTHALEIN TEST AND URINARY ANALYSIS.

By Ralph Colp, A.B., M.D.,
NEW YORK.

The following is a report of the effect of anesthesia and operation on kidney function as demonstrated by the phenolsulphonephthalein test and urinary analysis performed on 55 cases, selected mainly because of the objections raised to disturbing unnecessarily those cases which were to undergo or had undergone operations for involved intra-abdominal conditions.

The series comprises: 22 cases of hernia, 11 cases of chronic appendicitis, 6 cases of gynecological surgery, 3 cases of varicose veins, 3 cases of hemorrhoids, 3 cases of nephritic origin, 7 miscellaneous cases, as cholecystectomy, gastrectomy, cervical lymphadenectomy, hydrocele, sarcoma of the leg, carcinoma of the breast, and an orchidectomy. The cases were operated upon by the second surgical division of the Presbyterian Hospital.

The Routine. The routine followed was to have the patient drink four glasses of water, usually at fifteen minute intervals, so as not to cause nausea, and then at the end of the hour previous to the injection, have him void so as to insure the emptyness of the bladder. One cubic centimeter of the phthalein dye was then injected subcutaneously into the triceps region of the arm, and a sample of urine taken every few minutes until the characteristic red color appeared in the urine which had been previously rendered alkaline by the addition of a few drops of a 25 per cent. solution of sodium hydroxide. The time of the first appearance was noted and the urine excreted, collected for that hour, and the succeeding one, in separate bottles. The usual technic of diluting the specimen to 1 liter after it has been alkalinized was followed, and a sample read as soon as possible by the Helliges colorimeter by artificial light, it having been found that the matching of the intensity of color was better made thereby.

In cases in which doubt existed as to bladder retention the patient was always catheterized; in fact, 30 of the 33 males were catheterized at the end of the second hour, and whenever the color did not appear in fifteen minutes, a catheter was introduced, provided that there was urinary retention. The 22 female cases were all catheterized, the catheter being left in the urethra until the test was completed. About thirty-six hours after operation a second injection was made, the only exception being that sometimes the patient was unable to drink the full four glasses of water because of its nauseating effect after operation and anesthesia.

In addition a twenty-four hour specimen of urine was collected before operation and one after, an attempt being made to secure a better view of the activity of the kidney. The specimen was measured and described, its reaction and specific gravity noted, an albumin test performed, and a portion centrifuged and examined especially for casts.

The Anesthetic. The anesthesia employed was ether in 47 cases, given by the Bennet inhaler, previous to which a bag of nitrous oxide was administered; gas and oxygen in 7 cases given by the Luke apparatus; local anesthesia in 1 case with novocain 1 per cent.

THE AVERAGE PHTHALEIN EXCRETION.

In 47 ether cases the average ante-operative phthalein was	57.9 per cent.
Average p. o. phthalein	57.3 per cent.
Decrease	.6 "
In the 7 gas and oxygen cases the average ante-operative phthalein was	52.2 per cent.
Average p. o. phthalein was	49.0 "
Decrease	3.2 "

The Urine Analysis. The urine analysis showed 15 cases having albumin, 2 of which showed casts, or albumin present in 27 per cent. of the cases; of these 10 showed albumin after operation, 6 with casts. Ten cases, previously negative, developed albumin after operation, practically every one of these cases showing many hyaline and finely granular casts, or 25 per cent. of the previously negative urines showed some passing effect of kidney irritation.

EFFECT OF LENGTH OF ETHER ANESTHESIA AND OPERATION ON KIDNEY FUNCTION.

8 anesthesias lasting fifteen to twenty-nine minutes:	
Average a. o. phthalein	52.3 per cent.
Average p. o. phthalein	58.5 "
Increase	6.2 "
2 cases showed a trace of albumin with casts (postoperative).	
10 cases lasting thirty to forty-four minutes:	
Average a. o. phthalein	58.8 per cent.
Average p. o. phthalein	58.8 "
No change.	
4 cases showing albumin, 3 with casts (postoperative).	
11 cases lasting forty-five to fifty-nine minutes:	
Average a. o. phthalein	58.4 per cent.
Average p. o. phthalein	57.1 "
Decrease	1.3 "
7 cases showing albumin, 5 with casts (postoperative).	
11 cases lasting sixty to seventy-four minutes:	
Average a. o. phthalein	58.8 per cent.
Average p. o. phthalein	57.9 "
Decrease	.9 "
4 cases showing albumin, 1 with casts (postoperative).	

4 cases lasting seventy-five to eighty-nine minutes:

Average a. o. phthalein	50.8 per cent.
Average p. o. phthalein	40.8 "
Decrease	10.0 "

3 cases showing albumin with casts (postoperative).

Showing probably that as the length of anesthesia is prolonged the functional activity of the kidney is depressed, while in the shorter cases there is practically no change, perhaps even a mild degree of stimulation.

Effect of Age and Anesthesia on Kidney Function.

Below 20 years, average a. o. phthalein	64.1 per cent.	p. o. 61.5 per cent.
Below 20 to 39 years, average a. o. phthalein	56.0 "	p. o. 57.3 "
Below 40 to 59 years, average a. o. phthalein	52.8 "	p. o. 51.8 "

Showing mainly that as the age in years increases that the threshold activity of the kidney is diminished.

Effect of Type of Patient and Anesthesia on Kidney Function. That the kidney is affected by psychic influence and individual variation is well known, and it is partially illustrated in the figures given below.

I. Normal or average type:	
a. o. phthalein	58.7 per cent.
p. o. phthalein	59.8 "
Increase	1.10 "
II. Nervous type:	
a. o. phthalein	60.5 per cent.
p. o. phthalein	56.0 "
Decrease	4.5 "
III. Obese type, which, as a rule take anesthesia very poorly with cyanosis:	
a. o. phthalein	56.6 per cent.
p. o. phthalein	44.9 "
Decrease	11.7 "
IV. Anemic type:	
a. o. phthalein	55.5 per cent.
p. o. phthalein	46.0 "
Decrease	9.5 "
V. Arteriosclerotic type:	
a. o. phthalein	53.5 per cent.
p. o. phthalein	50.7 "
Decrease	2.9 "

The Ether Cases Individually. While the averaged case of ether anesthesia shows but little change the cases considered individually vary considerably one way or the other.

Twenty-two cases showed an increased postoperative phthalein of about 11 per cent. Ante-operative urine examination was negative in 17 of these cases and pathological in 5 cases or 22 per

cent., these 5 cases showing albumin but no casts. The postoperative urine examination of this series was negative in 15 cases, pathological in 7 cases, 3 cases previously having no abnormality now showing albumin, 1 with hyaline casts.

Twenty-two cases showed a decreased postoperative phthalein of about 16 per cent. average. The anteoperative urine examination was negative in 13 of these cases; pathological in 9 or 41 per cent.; 7 of these cases showing a faint trace of albumin, 2 with casts, and 2 cases showing a heavy trace of albumin and no casts. Postoperative urine examination of this series was negative in 8 cases, pathological in 14,6 cases of the 9 already mentioned showing further changes, 3 cases showing a greater albumin reaction, 4 cases now for the first time showing casts. Eight cases previously showing no urinary change now showed pathological elements, 1 case with a faint trace of albumin with casts, 4 cases with a moderate trace of albumin, 1 with casts, and 3 cases with a heavy trace of albumin, all with casts.

Within this group were 2 cases of nervous temperament which gave no urinary change, but marked phthalein postoperative deficiency; 1 other case was especially cyanotic, and had previously had Magendie solution ℥vj, leaving 2 cases which showed a decreased postoperative phthalein with no explanation or rather an attempt at one.

While the series of cases is small, it seems reasonable to suppose that preëxisting conditions of albuminuria predispose to a lowering of kidney efficiency as shown by the phthalein test after operation and anesthesia; and that in the majority of cases showing a decrease output, there is an accompanying urinary picture showing the effects of kidney irritation, rather mild in nature. That this is not permanent, is shown by a third phthalein test in 5 of the cases which suffered a severe depression, where in ten days time the kidney output was practically restored to what it was originally, and the urine examination was once more negative, or in the condition it was, before anesthesia.

The Gas and Oxygen Cases. Although there were but 7 cases of gas and oxygen, they show very interesting results.

In 2 cases of anesthesia of thirty-five and forty-five minutes respectively with an ante-operative phthalein of 51 per cent., and a postoperative phthalein of 47 per cent., a decrease of 4 per cent. occurred; one of the patients was of the nervous type and the other was a case of cardiovascular disease.

There were 4 cases of anesthesia of sixty, sixty-six, seventy, and a hundred and ten minutes with the average ante-operative phthalein excretion of 54 per cent., and a postoperative phthalein of 54 per cent., showing in one case only a faint trace of albumin after operation.

The seventh case was an anesthesia of a hundred and fifty minutes

with a decreased output postoperative of 14 per cent., the urine showing a trace of albumin and many hyaline casts.

Comparing this with the results obtained from ether anesthesia, in 3 of the cases which were very nervous, the average ante-operative phthalein was 55 per cent., the postoperative phthalein, 54 per cent., or a difference of 1 per cent. as compared with the difference of 4.5 per cent. in the ether series of nervous patients.

Summary and Conclusions. Upon the whole, the average case after thirty-six hours postoperative shows very little change in kidney function as demonstrated by the phenolsulphonephthalein test, although 25 per cent. showed urinary changes, which in ten days time were again negative.

The functional activity of the kidney is depressed as the length of anesthesia is increased, while in short anesthesias the kidney might even appear to be stimulated to a slight degree.

As age increases the threshold activity of the kidney is lessened.

Nervous patients, anemic, obese, and arteriosclerotic patients as a rule, show some effect of their physical or psychic state on kidney function.

Preëxisting conditions of albuminuria have a tendency to decreased phthalein excretion, and those cases which have a decreased phthalein excretion, in the majority of instances, show effects of kidney depression as evidenced by careful urinary analysis, although these effects are only temporary.

For long anesthesias and apparently for nervous patients, gas and oxygen as an anesthetic seems to have the least irritating effect on kidney function, as demonstrated especially by urine examination.

AN UNUSUAL DISORDER OF THE CARDIAC MECHANISM RELIEVED BY SURGICAL OPERATION.

By Edward B. Krumbhaar, M.D., Ph.D.

PHILADELPHIA.

(From the Medical Division of the Hospital of the University of Pennsylvania, Philadelphia, Pa.)

From the two points of view the following case is of interest, as an example, (1) of an unusual type of disordered mechanism of the heart beat, and (2) of the efficacy of removing cryptic or frank sources of reflex damage to the cardiac mechanism.

History. A. R., a married woman, aged fifty-six years, was admitted to the surgical wards of the University Hospital for repair of cystocele and rectocele. On physical examination, however, the pulse was found to be so distinctly irregular that the operation was

postponed. The following pertinent facts were obtained from the past history and examination:

The patient has never had any cardiac symptoms further than slight attacks of palpitation for several years, associated with indigestion and flatulence. For the past two years she has noticed some slight dyspnea on exertion, but never any edema or chronic cough. She did not know that her pulse was irregular. The pelvic symptoms—pain in right side of abdomen and a palpable mass in the vagina—have been present for two years. She has had four healthy children and one miscarriage (probably from overexertion). Aside from the coupled beats and pelvic disorders, physical examination revealed nothing of importance. The heart was of average size and the sounds normal. At times there was a pulse deficit of 50 per cent., due to the second beat of each couple failing to reach the wrist, but this beat was always sufficient to raise the aortic valves. There was no congestion, edema, or other signs of myocardial weakness. The urine showed a normal specific gravity, a faint trace of albumin, but no casts. Blood examinations were negative.

An electrocardiogram taken at this time revealed (Fig. 1) a condition of coupled beats, that on superficial examination might be mistaken for nodal rhythm coupled with regularly recurring extrasystoles arising from a part of Tawara's node other than that responsible for the nodal rhythm. The arrhythmia was later considered, however, to be due to auricular extrasystoles coupled with normal beats, both being followed by an unusually short conduction time. The basis for these interpretations will be discussed later. The atropin test (2 mgms. hypodermically) failed to affect the "coupled" rhythm, although the cardiac rate was raised from 92 to 118 beats per minute. Digitalis medication (0.67 c.c. of the tincture four times a day) succeeded after six days in lengthening the *P-R* interval to 0.16 second, but the premature contractions continued to appear almost constantly in the form of "pulse bigeminus."[1] (It is perhaps noteworthy that the *P-R* interval of the first cycle of each pair began to lengthen after three days of digitalis, whereas the second cycle required eight more doses before it was affected.)

As the arrhythmia had been found not to be of serious import, the contemplated surgical operation was performed with uneventful success. The pulse-rate did not go beyond 106 at any time during the operation, and was noted as regular during the period of anesthetization. This regularity continued during convalescence, and an electrocardiogram taken at that time showed that a normal mechanism existed (Fig. 2). As the influence of digitalis wore off the shortening *P-R* interval did not return to its former position beyond

[1] The influence of digitalis on the form of the T-wave (Cohn, Jour. Exp. Med., 1915, xxi, 593) is fairly well demonstrated in this case.

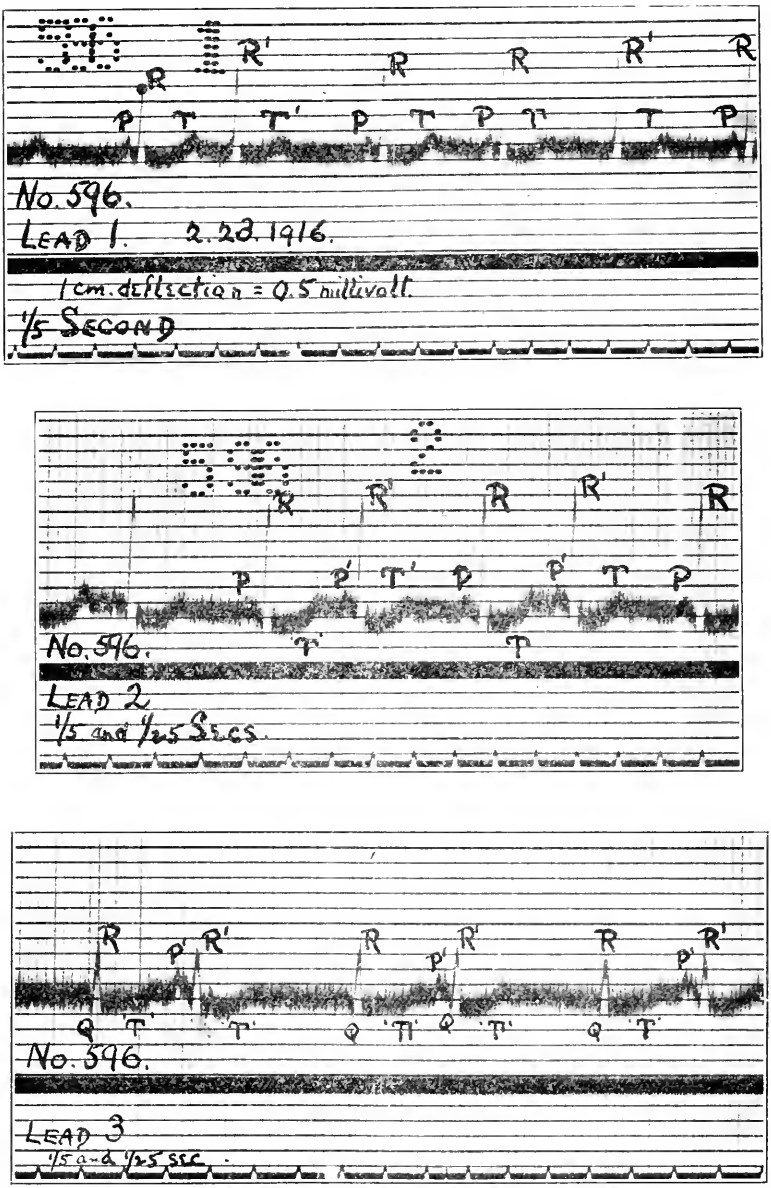

Fig. 1.—Electrocardiograms from the three customary leads, showing shortened *P-R* interval and "pulsus bigeminus," due to recurring auricular extrasystoles. Note that the *P* of the second cycle of each pair is of slightly different form from that of the first. In Lead 1 the ectopic P-wave and in Lead 3 the normal P-wave are not plainly distinguishable, but were present in other records taken during the period of bigeminy. The *P-R* interval is 0.10 and 0.09 second respectively. (Normal *P-R* interval 0.12 to 0.17 second.)

the shorter normal limits, and when the patient was last seen the ectopic beats had not reappeared. The patient continued in good

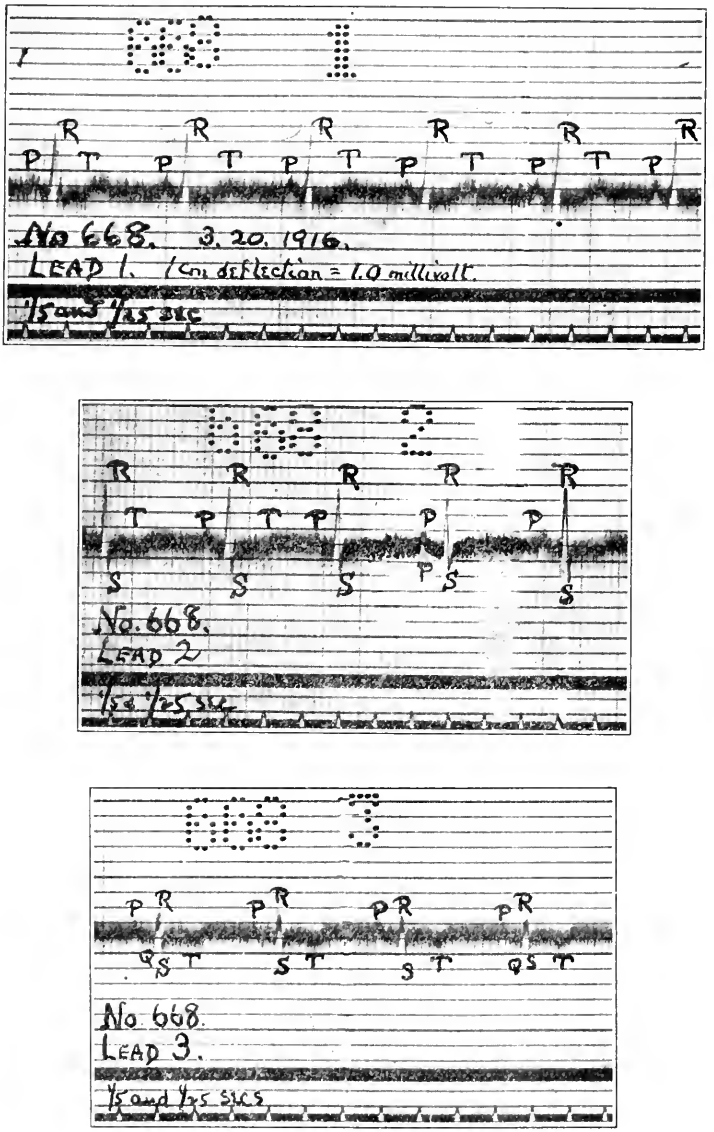

FIG. 2.—Electrocardiograms showing normal rhythm. Note absence of ectopic beats and that the *P-R* interval is now within normal limits (0.12 second).

health, gained weight, and during the period of observation had no cardiac symptoms of any kind. It is regrettable that the patient

cannot return for future study, so that it is impossible now to say whether or not the return of the cardiac mechanism to normal rhythm has proved permanent.

The preliminary interpretation of nodal extrasystoles added to nodal rhythm was based on the very short *P-R* intervals (0.10 and 0.09 second), thus fulfilling one of the two necessary requirements for the diagnosis of ectopic beats arising in Tawara's node,[3] namely, either that auricle and ventricle should contract simultaneously or that the conduction time should be distinctly shortened (normal *P-R* interval being 0.12 to 0.17 second). The other requirement—that *P*, the sign of auricular activity, should be of altered form—is only imperfectly shown in the second beat of each pair and not at all in the first. (The nervous condition of the patient rendered it impossible at any time to obtain records free from tremors.) In several cases in the literature a rhythm made up of cardiac cycles similar to the first one of each of these records has been called "nodal rhythm," in spite of the fact that Lewis and others have shown that impulses arising at an appreciable distance from the sinus node cause diphasicity or inversion of the *P* wave. A case recently observed at the Presbyterian Hospital of New York[4] demonstrates that at least some cases of apparent nodal rhythm with upright *P* are in reality due to a prolonged *P-R* interval equal in length to the interval of a cardiac cycle, so that *P* of one cycle falls on *R* of the preceding cycle. Whether true nodal rhythm can occur without obvious changes in the form of *P* is a point that is well worth studying experimentally.

In the present case, however, the gradual lengthening of the *P-R* interval under the influence of digitalis without change in the form of *P*, proves that the unusually short *P-R* interval of both cycles was due not to ectopic impulses arising in Tawara's node, but to lessened conduction time of impulses arising in the sinus node and an ectopic site in the auricle respectively. As the chief factor in the production of the *P-R* interval is the delay caused by the passage of the impulse through Tawara's bundle,[5] one must assume that the shortened interval of this case was due to positive dromotropic influences on this structure, and that these influences disappeared with repair of the pelvic disorders, as did the bathmotropic influences that caused the auricular extrasystoles. About the possible causes of such an increased conductivity, however, there is practically no evidence at hand, either clinical or experimental.

SUMMARY. A case of cardiac arrhythmia is described in which a condition of ectopic beats arising in different parts of Tawara's node was simulated by a shortened conduction time (*P-R* interval) with recurring auricular extrasystoles (pulsus bigeminus).

[3] Lewis, Thomas: Clinical Electrocardiography, p. 50.
[4] Personal communication from Dr. Strong.
[5] Hering, H. E.: Arch. f. d. ges. Phys., 1909–1910, cxxxxi, 572.

Both of these disorders of the cardiac mechanism were relieved by a pelvic operation (anterior and posterior colporrhaphy), at least to the extent that they disappeared during the period of observation.

My thanks are due to Dr. C. C. Norris for permission to study this case.

LEAD POISONING IN CHILDREN WITH ESPECIAL REFERENCE TO LEAD AS A CAUSE OF CONVULSIONS.[1]

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We are indebted to the Australian writers Gibson, Love, Turner, Breinl and Young and others for much of the recent literature regarding lead poisoning in children. They have had an unusually good opportunity to study this condition. Thus, in the Brisbane Children's Hospital, 76 cases were seen in five years and Gibson himself observed 24 cases in six years.

I shall not attempt to give a complete review of the literature on the subject, as the chief object of this communication is to draw attention to lead as a cause of convulsions in children and to report 4 cases seen in Dr. Howland's clinic at the Harriet Lane Home, the Johns Hopkins Hospital. For the more important articles, the reader is referred to those from which I have freely quoted.[2]

The symptoms of lead poisoning vary according to the susceptibility of the child and to the duration of the infection. The degree of susceptibility is variable. Breinl and Young refer to many instances in which only one child in a family was affected, although the other children were exposed to the same influences. In other instances, one child reacted with pronounced symptoms while the only evidence of infection in the others was a blue line on the gums.

Gibson[3] considers the ingestion of lead as the most likely source of infection, although he appreciates that it may occur from the inhalation of dust containing lead. He points out that children

[1] From the Harriet Lane Home, Johns Hopkins Hospital, and the Department of Pediatrics, Johns Hopkins University.

[2] Gibson, Love, Hardie, P. Bancroft, Jeffris Turner: Notes on Lead Poisoning as Observed in Children in Brisbane, Intercolonial Medical Congress of Australasia, Sydney, 1892, p. 76. Gibson, Lockhart: Ocular Neuritis Simulating Basal Meningitis Plumbism, Australasian Med. Gaz., October 20, 1897, p. 479. A Plea for Painted Railings and Painted Walls of Rooms as the Source of Lead Poisoning Among Queensland Children, Australasian Med. Gaz., 1904, xxiii, 149. The Importance of Lumbar Puncture in the Plumbar Ocular Neuritis of Children, Tr. Australasian Med. Congress, 1911, ii, 750. Breinl and Young: The Occurrence of Lead Poisoning Among North Queensland Children, Ann. Trop. Med. and Parasitol., 1914–15, viii, 475. Turner, Jeffris: Lead Poisoning Among Queensland Children, Australasian Med. Gaz., 1897, October 20, p. 475.

[3] A Plea for Painted Railings and Painted Walls of Rooms as the Source of Lead Poisoning Among Queensland Children, Australasian Med. Gaz., 1904, xxiii, 149.

who bite their fingernails and suck their fingers are much more frequently affected, and believes that their hands became contaminated with dried paint from porch railings and houses. That poisoning may occur through inhalation has been shown by the experiments of Goadby and Goodbody[4] and by Legge and Goadby.[5] They conclude that the danger from inhalation is far greater than from the ingestion of lead. While this, no doubt, is true among workers in lead, the swallowing of lead in some form is probably the more common source of the poisoning in children.

In the early cases a change in disposition is often the first symptom which is noticed. The child becomes fretful, peevish, and often very restless at night. The appetite becomes poor, the breath foul, and frequently hemorrhages occur from the gums. The child may complain of pain in the epigastrium and legs.

In the cases of longer duration the pains in the abdomen become continuous and more severe. Constipation is present, as a rule. Vomiting rarely occurs. The muscles are often so painful as not to permit of the weight of the bed-clothing. The gait of the patients is described as being characteristic. It is a waddling gait; they walk on the outside of the feet, the toes are dragged, and with each step the legs are swung sideways before the feet are put to the ground. Occasionally the parents' attention may be attracted by one or more of the many indefinite signs enumerated above, but not infrequently nothing abnormal is noticed until the development of cerebral disturbances. The cerebral manifestations will be referred to later.

Very few of the cases reported by Breinl and Young showed the characteristic wrist-drop so common in adults. This has been the experience of others, and generally the paralysis first affects the legs in children. A paralysis much like that of the Aran-Duchenne type occurring in muscular dystrophy has been reported in 2 cases. Paralysis of the cranial nerves is very common; the facial and the motor oculi nerves, either entire or in part, are those most frequently involved.

Gibson[6] has reported a most interesting group of eye symptoms which he refers to as a "plumbic ocular neuritis." The neuritis usually occurs in children below the age of eight years. There may be an optic neuritis, with retinal hemorrhages, or an optic atrophy. There is an accompanying weakness of one or both external recti muscles. He has seen as many as 9 such cases in a year, but in the 22 cases reported by Breinl and Young only 1 patient was so affected.

[4] Seventh International Congress of Applied Chemistry, 1909, Section VIIIa, 306.
[5] Poisoning and Lead Absorption, London, 1912, p. 122.
[6] Ocular Neuritis Simulating Basal Meningitis Plumbism, Austral. Med. Gaz., October 20, 1897, p. 479. The Importance of Lumbar Puncture in the Plumbic Ocular Neuritis of Children, Tr. Austral. Med. Congress, 1911, ii, 750.

The temperature is, as a rule, normal, though it may be irregularly elevated. In the fatal cases, and especially those with cerebral disturbances, it may be high, reaching 105° or 106° before death.

Very often the clinical symptoms are not sufficient to warrant a diagnosis of lead poisoning. This is especially true in the early cases. However, when there are suggestive symptoms other evidences of the condition are usually to be found. Among these are the blue line on the gums and stippling of the red cells. Basophilic granulations are present in a small number of red blood corpuscles in the majority of the cases. The blood otherwise shows nothing characteristic, although there may be a secondary anemia. This apparently is determined by the duration of the poisoning.

Direct evidence of lead poisoning is obtained by the demonstration of lead in the urine or feces. In this connection the recent observations of Breinl and Young are most interesting. They examined eight children with early signs of the disease, *i. e.*, slight pains in the epigastrium and legs, but without basophilic granulations and the lead line, and found appreciable quantities of lead in the excreta. They found there was always a larger amount in the feces than in the urine, and that it was often present in the feces when it could not be demonstrated in the urine. Dixon Mann[7] found larger quantities of lead present in the feces than in the urine. Others have made this observation, and Legge and Goadby say that lead in the urine is not so common nor definite a symptom as supposed.

From the foregoing summary of the more common clinical signs seen in lead poisoning in children it is evident that a definite classification of the cases into different groups is difficult, and when made has to be based on the severity of the predominating symptom. For instance, one patient may present the characteristic picture of the disease, one may show only irritability and indefinite pains in the abdomen, whereas another may become paralyzed or may be seized with convulsions while in apparent health. In spite of the difficulties attendant upon establishing a classification for lead poisoning, Jeffris Turner[8] speaks of four main groups as follows:

1. Paralytic cases showing symmetrical wrist-drop and foot-drop; spasm of the calf muscles, and as a secondary lesion, a persistent talipes equinus; (2) cases characterized by pains in the abdomen and limbs, concomitant with habitual constipation, and an occasional blue line on the gums, the children becoming at the same time irritable and neurotic; (3) children suffering from ocular neuritis, a neuritis involving the optic, and at the same time the oculomotor nerves; (4) eclamptic cases suffering from severe and persistent convulsions which often end fatally.

In the cases reported from Australia, convulsions were observed

[7] Forensic Medicine and Toxicology, London, 1908, p. 487 (C. Giffin & Co.).

[8] Lead Poisoning Among Queensland Children, Australasian Med. Gaz., October 20, 1897, p. 475.

very infrequently, though mild cerebral disturbances were frequently present. That convulsions may occur in the course of lead poisoning, has been recognized since the observations of Stockhausen[9] in the seventeenth century. The first careful investigation of the cerebral disorders due to lead was made by Tanquerel.[10] He grouped them under the term Encephalopathia Saturnina. Though his researches were published in 1882, but little attention has been paid to the lead encephalopathies except as they are found in adults and in particular among workers in lead. Lead as a cause of convulsions in children has been ignored almost entirely, and especially among observers in this country.

An interesting and extensive series of cases with convulsions has been reported by Stewart,[11] They occurred among 64 cases of lead poisoning which he investigated in Philadelphia, due to eating buns colored with chrome yellow. Seven of the 16 cases in which convulsions occurred were in children between one and a half years and twelve years of age. Stewart believed that of the various forms of cerebral disorders produced by lead, the convulsive was by far the most common—that it formed two-thirds, if not more, of all the cerebral manifestations, and that it had the highest mortality. He (Stewart) thought it impossible to make any clinically exact systematic grouping of the different forms of the lead encephalopathies as Tanquerel[12] did, as one form merges into the other.

Stewart cites 2 cases of so-called idiopathic epilepsy which were secondary to convulsions, symptomatic of lead poisoning, and suggested that epilepsy of lead origin may be of much more frequent occurrence than is generally supposed.

The macroscopic changes most frequently found in the brain are an edema and anemia, with flattening of the convolutions. The brain may, however, be markedly congested. There is often a thickening of the pia—it may be adherent to the cortex. There may be hemorrhages into the pia and between the pia and the cortex. There is also a round-cell infiltration within the pia, and the neuroglia cells of the cortex are found to be increased. Spiller[13] observed a proliferation of the endothelial cells upon the surface of the cerebral pia. Such pathological findings may occur in other conditions, and similar lesions may be found in patients with lead poisoning who have not manifested cerebral symptoms.

There is no way by which the convulsive seizures *per se* in lead poisoning can be distinguished from those due to other causes. All types of convulsions are seen. They may be local or general.

[9] Quoted by Stewart (see note 11).

[10] Lead Diseases (translation by Dana, 1848), p. 263.

[11] Lead Convulsions, Am. Jour. Med. Sc., 1895, cix, 288.

[12] Tanquerel established the following divisions: (1) delirious forms; (2) comatose form; (3) convulsive forms; (4) above forms combined.

[13] Jour. Med. Research, 1903, x, No. 1.

They may be mild or severe. The convulsions in lead poisoning do, however, have certain peculiarities which appear to be characteristic of the disease. They are very persistent, they show a great tendency to recur, and they are attended by a high mortality.

The persistence of the convulsions is shown in Cases II and III. Enormous doses of bromides, chloral, and morphin were administered to each patient without causing any effect on the convulsions. It was only by the continued use of chloroform that they could be controlled, and when this was discontinued the convulsions began anew. In one patient (Case I) there were two recurrent attacks in a period of seven and a half months. The convulsions recurred after a period of eighteen days in another patient (Case II). With each recurrent attack they were severe, and were controlled only with chloroform. One patient (Case III) died in the first convulsive attack. The convulsions in one patient (Case IV) were mild, lasting only one day. He was delirious at first, then had convulsions, after which he was comatose for several days. The behavior of this patient serves to support Stewart's contention that it is not possible to define sharply the encephalopathies into definite groups.

The high mortality of convulsions due to lead is shown by Stewart's cases. The termination was fatal in 6 of the 7 children. A series of most remarkable cases reported by Berger[14] emphasizes the fatality of the condition equally well. In a pot-glazier's family, who lived day and night in an atmosphere saturated with lead fumes, the father suffered from the comatose variety of lead encephalopathy. Seven children died in convulsions, four others had frequent cerebral disorders and suffered from peripheral neuritis. Several of the grandchildren died in convulsions. In my series of cases 3 of the 4 patients died. The patient who recovered has not shown any evidences of a recurrence. One patient (Case I) died in convulsions during the third attack, another (Case II) during the second attack, and the other (Case III) during the first attack.

The temperature, which was normal on admission in two patients (Case II and Case III), preceding death rose to 107.5° and 105.5° respectively. Such a hyperpyrexia has been present preceding death from lead convulsions in most of the reported cases.

Evidences of cerebral involvement other than convulsions were present. In one patient (Case I) there was rigidity of the neck and a positive Kernig sign. He had also a paralysis of the left external rectus muscle of the eye. Another patient (Case IV) had rigidity of the neck and a temporary paralysis of the facial nerve.

Mosny and Malloizel[15] and Plate [16] and others have pointed out that there is very generally evidence of involvement of the meninges,

[14] Berl. klin. Wchnschr., 1874.

[15] La meningite saturnine, 1907, xxvii, 506.

[16] Ueber einen Fall von Meningitis saturnina, München. med. Wchnschr., 1913, lx, 2343.

as shown by the fact that the cerebrospinal fluid contains an increased number of cellular elements. In chronic lead poisoning they rarely found any change in the cerebrospinal fluid. In this series the spinal fluid from all the patients was examined and changes were found in three of them. In these three patients the spinal fluid was clear, not under increased pressure, and a fibrin clot did not form on standing. In two patients (Case II and Case III) the cellular elements were not increased, but there was a marked globulin reaction (Ross-Jones). In one patient (Case I) there were thirty cells per cubic millimeter, mainly lymphocytes, and a marked globulin reaction. The spinal fluid from this patient was examined on several occasions over a period of eight months, and on each examination there was an increase in cells and a positive globulin. In the fourth patient (Case IV) the spinal fluid was not examined until four weeks after he had recovered, and at this time it showed no changes other than twelve cells per cubic millimeter. Such a slight increase in cells does not signify a pathological change.

Eye changes during the course of lead encephalopathies have been noted by a number of different observers. Wilbrand and Sanger,[17] who have collected reports of most of the cases, believe that optic neuritis may occur primarily through the direct toxic action of lead on the nervous system or by the production of interstitial neuritis or through the alterations of the bloodvessels in the retina and optic nerves. It also may occur secondarily through intracranial changes or changes in the kidney. Gibson, as mentioned previously, has written extensively on the eye changes in children, and believes that they frequently occur without other symptoms of lead poisoning. In two of my patients (Case I and Case II) there were extensive hemorrhages into the retina and optic neuritis. In one (Case I) the condition gradually subsided and the eye grounds became normal after a month. At the time of his second admission there were retinal hemorrhages and a choked disk. The eye grounds were normal in the other two patients (Cases III and IV).

As a rule there are certain symptoms which precede the development of the convulsions. These may be the common symptoms of plumbism or they may be so slight as to escape notice. Colic has been more frequently observed than paralysis or arthralgia, but more common are irritability, restlessness, and a blue line on the gums. Vomiting and constipation are not infrequent, and many patients complain bitterly of pain in the head. In two patients (Case I and Case IV) of this series there was an interval of several days before the convulsions, when the children were irritable during the day and restless at night. One of them complained of headache, and they both had attacks of vomiting. In one instance (Case III) the indefinite symptoms covered a period of about three months. There

[17] Die Neurologie des Auges, 1913, vol. v.

was evident impairment of general health with frequent attacks of vomiting and colic. At times the onset of convulsions is sudden.

The duration of the period between the first exposure to lead and the development of cerebral symptoms is variable. The exact time of the exposure in the patients of this series could not be determined with certainty. Three of them (Cases I, II and III) had been exposed for many months, as the source of the infection was found to be from eating paint. In one patient (Case IV) the source of lead was not ascertained.

In addition to the symptoms preceding the convulsions the patients in this series showed other evidences of lead poisoning. The blood picture was that of a moderate secondary anemia, and in all a few red blood corpuscles showed basophilic degeneration. In the four patients there was a leukocytosis of about 20,000, with a moderate increase in the polymorphonuclear cells. The blue line on the gums was present in three of the four patients (Cases I, III, IV). It should be remembered that a continuous lead line is seldom found. The characteristic appearance is the presence of minute black dots in the margin of the mucous membrane around the teeth which are covered with tartar. It is difficult to see and without the aid of a hand lens may readily be overlooked.

Efforts made to determine lead in the urine of two patients (Cases I and II) were unsuccessful. The feces were not examined.

The following are brief histories of the 4 cases which form the basis for this report:

Case I.—The patient, W. M.,[18] aged five and one-half years, complained first of pain in his head, and was very restless at night. The following day he vomited several times, and it was noticed that his neck was stiff. He appeared very ill, became rapidly worse, and on the fourth day of his illness severe generalized convulsions began. On the fifth day, August 22, 1913, he was brought to the hospital in a comatose state. He continued to have recurrent generalized convulsions, his neck was retracted, and there was an internal strabismus of the left eye. There was an optic neuritis and a hemorrhagic retinitis on the right. The left optic nerve was normal. The temperature was normal. The leukocytes were 27,600. The spinal fluid obtained on four occasions was clear and sterile. It was under slightly increased pressure at the first spinal puncture, but subsequently the pressure was normal. There were from twenty to forty cells per cubic centimeter (mostly mononuclears). The Noguchi globulin reaction was positive. The Wassermann (blood) was negative. The convulsions ceased after the first lumbar puncture, but he remained in coma for the next two days. He gradually improved and after a week seemed nearly well. The convulsions did not recur and he was discharged

[18] This case was reported by Thomas and Blackfan: Am. Jour. Dis. Child., 1914, viii, 377.

September 20, 1913. The abnormal changes in the right optic nerve gradually subsided, but the spinal fluid contained an increase in cells and a positive globulin reaction. With the exception of an occasional attack of vomiting and abdominal pain, he remained in excellent condition for five months.

On March 1, 1914, he complained of headache and he vomited. The convulsions recurred, and on March 3 he was again admitted to the hospital. His condition was almost identical with that at the time of the first admission. There were generalized and persistent convulsions, a definite rigidity of the neck, and an optic neuritis and hemorrhagic retinitis of the right eye. At this examination the characteristic lead line was seen on the gums. The red blood corpuscles were 4,480,000, the white blood corpuscles 23,000, and the hemoglobin 55 per cent. There was well-marked stippling of the red blood corpuscles (Grawitz granules). No lead could be demonstrated in the urine. The convulsions subsided after lumbar puncture. Two or three days after admission an internal strabismus of the right eye developed. The patient made an uneventful recovery and was discharged on May 1.

He remained in apparently good health for three weeks, when on May 25 he had a severe convulsion and died. No postmortem examination was obtained. The source of the lead was determined when his lips were found covered with white lead paint which he had nibbled from the railings of his crib. On investigation at the orphanage where he lived it was found that the white paint on his bedstead had been entirely gnawed off.

Case II.—R. B. (7094). This patient was aged two and one-half years. On March 8, 1915, he had a convulsion which lasted about two hours. From then until March 12 he seemed well. On the morning of March 12 convulsions began about 7.30. He was brought to the hospital at noon the same day in convulsions, which continued for about twenty-four hours. These convulsions involved the eyes, the left side of the face, and the left arm. He had no fever. There was a leukocytosis of 19,000. The red blood cells were 4,000,000. Hemoglobin, 50 per cent. There was well-marked stippling of the red cells.

On examination the positive findings were a lead line about the upper and lower teeth and an enlarged spleen. He was entirely relaxed between the convulsions, the reflexes were not exaggerated, and Kernig's sign was absent. The eye grounds were normal. The spinal fluid was clear and not under pressure. There were seven cells per cubic millimeter and a positive globulin reaction. Examination of the urine for lead was negative.

The child had no convulsions in the hospital, and was discharged on March 25. He was brought back to the hospital on March 26, twelve hours after discharge, in a convulsion which involved the face and the left arm. He continued to have convulsions for twenty-four

hours in spite of energetic treatment with morphin, chloral, and bromides. By the administration of chloroform the convulsions could be checked, but they recurred as soon as it was discontinued. The temperature rose to 107.5° just before death.

Source of Lead. The father stated that the child would gnaw any painted article, and that he and his brother had recently ruined a set of parlor furniture by eating the paint from it.

CASE III.—(9182) H. B., aged two years. A brother (R. B., Case No. II) died in the Johns Hopkins Hospital of lead poisoning March 27, 1915.

The patient was a normal child, and was well until he had varicella at sixteen months. Shortly after this he complained of pain in the abdomen and was operated on by an orthopedist for appendicitis (February, 1915). The appendix was normal. For two or three months preceding the onset of his acute illness he was not well. He often vomited and complained a great deal of abdominal pain. He vomited more than usual on October 15, 1915, and at 11 P.M. had a convulsion. The convulsions continued, and he was admitted to the hospital the following day, October 16. The patient was comatose on admission and was having repeated and severe convulsions. The convulsions were general in character, with possibly greater involvement of the right than the left side of the body. The neck was not rigid; there was no Kernig's sign. The knee-kicks were not obtained. Examination of the mucous membrane about the teeth failed to show a lead line.

Ophthalmoscopic Examination. Right: The margin of the disk was obscured. The vessels were full and tortuous; there were small retinal hemorrhages. Left: The margin of the disk was obscured by a large retinal hemorrhage, and there were other hemorrhagic areas throughout. The leukocytes were 20,000. The red blood cells were 3,600,000 and the hemoglobin was 55 per cent. Many stippled red cells were present. The spinal fluid was clear and not under increased pressure. There were nine cells per cubic millimeter and the reaction for globulin was positive.

Course in Hospital. The convulsions persisted in spite of enormous doses of chloral and morphin. It was only possible to control them by the use of chloroform. This, however, was of temporary benefit, as the convulsions commenced again when it was discontinued. The patient did not regain consciousness. The temperature, which was 97.6° on admission, gradually rose, and just before death reached 105.5° (fifteen hours after admission).

Source of Lead. Same as in Case II.

CASE IV (8491).—J. N., aged three years. The patient, the older of two children, was of normal development and, with the exception of pertussis at two years, had always been well. There was no history of convulsions. The present illness began acutely on July 30, 1915, with drowsiness. He slept the greater part of that

day, was very weak, refused his food, and vomited. At night he was delirious. He jumped out of bed, cried out several times, and threw his head back as though in pain. The next day, July 31, he appeared better, though still weak and drowsy. Again, at night, he became delirious and had several attacks of crying and throwing his head back. On August 1 he was comatose, and he had several convulsions. He did not improve, and was admitted to the hospital August 2.

The temperature on admission was 101°, pulse 124, respirations 20. He lay quietly in bed, with his eyes closed, and made no effort to speak. He was well-nourished and did not appear very ill. The neck muscles were slightly rigid and attempts to flex the neck caused pain. The reflexes were active but not increased. The examination of the heart and lungs was negative. The spleen was palpable. There was a well-marked lead line present in the mucous membrane about several of the upper teeth. It was especially well defined about the upper lateral incisors. The optic discs were normal.

The red blood corpuscles showed stippling in a few cells. The white blood corpuscles were 7500 per cu.mm. The differential count was:

	Per cent.
Polymorphonuclears	67
Small mononuclears	20
Large mononuclears	6
Transitionals	2
Polymorphonuclear eosinophiles	5

The Wassermann (blood) was negative.

Course in the Hospital. The child lay in a semistupor for most of the day after his admission. He was easily aroused, and at times appeared conscious but would not speak. The respirations were full and deep, varying between eighteen and twenty-four. They were irregular, and a few periods of apnea were observed. There was a well-marked tâche cérébrale, and Kernig's sign was suggestive. The neck was rigid. The condition remained the same for the next two or three days. There were no convulsions. On August 5 the patient seemed much better. He sat up in bed and could walk when placed on his feet. On this day an incomplete paralysis of the right facial nerve was observed. Improvement in his condition continued. The temperature gradually became normal, and six days after (August 8) admission he appeared quite well, except that he was very weak. The facial paralysis slowly became less marked, and it disappeared after about ten days. When he was discharged on August 12 (ten days after admission) he was apparently well.

A lumbar puncture was made several times during his stay in the hospital, but blood was obtained each time, and for this reason a cytological examination was not made. Four weeks after the onset,

when the child was apparently well, the spinal fluid was clear, not under increased pressure, and contained twelve cells per cubic millimeter. The globulin reaction at this time was positive. The source of lead was not determined.

Case.	I.—W. M. 2 years.	II.—H. B. 2½ years.	III.—R. B. 2 years.	IV.—J. N. 3 years.
Onset of convulsions	4th day	1st day	2 to 3 mos.	3 days.
Leukocytes	27,600	20,000	19,000	19,500
Spinal fluid:				
Cells	30	9	7	12 [19]
Globulin	+	+	+	0
Temperature, on admission	99.4° F.	99° F.	97.6° F.	101° F.
Lead line	+	0	+	+
Stippling red blood cells	+	+	+	+
Eye	Hemorrhagic retinitis; choked disk	Same as Case I	Negative	Negative.
Neurological	External rectus palsy; convulsions; coma; rigidity of neck	Convulsions; coma	Convulsions; coma	Delirium; convulsions; coma; rigidity of neck; facial paralysis.
Source of lead	Eating paint	Eating paint	Eating paint	Not known.
Result	Died	Died	Died	Well at present time.

Conclusions. In conclusion, I would urge that energetic prophylactic measures be taken with children who habitually eat painted articles in order to guard against the development of lead poisoning. Since my attention has been directed to lead poisoning I have found a number of children who nibble the white paint from enameled cribs.

In all patients with convulsions in which the etiological factor is not clear, lead should be suspected. This can be readily determined, as in the majority of instances there are other evidences of the condition, *e. g.*, the lead line, basophilic degeneration, and the presence of lead in the feces.

The examination of the spinal fluid may prove to be an index as to the seriousness of the affection and of prognostic aid. In three of the four patients changes were found. In one patient (Case I) changes were present in the spinal fluid for many months, and the patient eventually succumbed. In another patient (Case IV) who has recovered, and in whom the convulsions were not severe, the spinal fluid could not be examined at the time of the convulsions. Four weeks later the spinal fluid contained twelve cells and the globulin reaction was normal.

[19] Four weeks after the convulsion.

PRIMARY ENDOTHELIOMA OF THE PLEURA.

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(From the McManes Laboratory of Pathology, University of Pennsylvania.)

The purpose of this paper is to report in full a case of endothelioma of the pleura. I am indebted to Dr. Alfred Stengel for permission to use the case, and the very excellent history is the product of his staff at the University Hospital. I may be forgiven for including considerable detail in the pathological protocol in view of the fact that the condition is not rare but relatively uncommon and the opportunities for studying the cases in full have evidently not been numerous.

In reviewing the records of the pathological department, comprising over 5000 reports, I have found 9 cases, a report of which will appear later. According to Clarkson, out of 10,000 autopsies in the Pathological Institute at Munich, only 2 cases of primary endothelioma were found. He obtained from the literature 41 cases. I have made no attempt to cover all of these cases, but in reviewing a few of them several points may be noted: There has been some confusion between the primary sarcoma and primary endothelioma, and in some cases this is merely in the use of terms. The older writers are meager in their descriptions, but they mention the resemblance to carcinoma, so that by some the term "endothelial cancer" is used. It would seem that the growth occurs either as one large mass, usually posterior in position, infiltrating the lung, or as several small nodules, confined to and scattered over the pleura. Both pleuræ are involved, often with dense adhesions, and fluid. Metastases are common but not widespread. The diagnosis before autopsy is always difficult, with the possibility of tuberculosis and aneurysm as factors. Absence of temperature and negative sputum, with progressive dyspnea, weakness, loss of weight, and signs pointing to consolidation in the chest without pain, seem to be the predominating factors from the records I have been able to consult.

Case History.—J. M., white, American, salesman, was admitted to the University Hospital April 4, and died April 30, 1914. He complained of loss of weight, weakness, and constipation. His present illness began sixteen months ago with a vomiting spell. This was not accompanied by pain. Dizzy attacks soon followed. Six months later he noticed a loss of voice, a hacking, nonproductive cough, belching of gas, and vomiting every day after meals. He then began to progressively grow weaker, with loss of weight. During the past ten months he has lost forty pounds. For the past month night sweats have been constant, with a cough now associated with expectoration of a mucopurulent character. He

sleeps poorly, his appetite is failing, is constipated, and requires cathartics.

The patient stated that his father died of tuberculosis and one brother of Bright's disease. He denied syphilis, and has always been well until his present attack.

It was noted upon physical examination that he was amaciated, with a pale, warm, moist and sallow skin. The superficial lymph nodes were palpable. The radial pulses were equal, synchronous, and of good volume and tension. The arterial walls were sclerotic. The right pupil was more dilated than the left, and both reacted to light and accommodation. The tongue was dry and coated, with a slight pyorrhea of the gums.

In the thorax the expansion was poor. The spine was tender to pressure over the upper dorsal region. The ribs and clavicles were prominent, with deep supra- and infraclavicular fossæ. Anteriorly, both apices were dull, with the breath sounds bronchial in character, fremitus increased, an occasional rale, bronchophony and pectoriloquy. The breath sounds elsewhere were harsh, with prolongation of expiration. Posteriorly, both apices were dull as far as the middle of the scapulæ. Over this area the breath sounds were harsh. At the left base upon deep inspiration there was a "cogwheel" breath synchronous with the pulse.

The blood-pressure was systolic 120 and diastolic 75. The heart sounds were of good quality and tone; the first apical sound was loud, the second valvular, the aortic and pulmonary, especially the latter, were accentuated.

As to the extremities the reflexes were increased. The left leg was extremely amaciated. The left thigh upon flexion was 1.5 cm. smaller than the right. Pain was present in the hip-joint upon motion.

The following notes were observed from day to day:

April 5. Urine analysis: no albumin, sugar or casts. Blood: hemoglobin, 74 per cent.; red blood cells, 4,700,000; white blood cells, 8000; polynuclears, 70 per cent.; lymphocytes, 28 per cent.; large mononuclears, 2 per cent. The feces were streaked with blood and mucus.

April 6. The pupils were equal today. The sputum was negative for tubercle bacillus.

April 7. It was noted by Dr. Stengel that the right pupil was dilated; dulness to percussion was distinct anteriorly and posteriorly on the left.

April 8. Urine analysis: no sugar; a trace of albumin with light and dark granular and hyaline casts. A second specimen of sputum was negative for tubercle bacilli. Occult blood was positive in the feces, with a faint trace of bile. Dr. Grayson noted upon laryngeal examination that the right vocal cord was free while the left was fixed and immobile. A rectal examination was negative.

April 9. The Wassermann was negative. The patient complained of pain along the right costal border, with tenderness upon palpation over the ascending colon. A cutaneous nodule in the abdominal wall is noted as increasing in size.

April 11. The examination of the eye-grounds was negative. The stomach was noted below the umbilicus. A test meal resulted as follows: total acidity, 40 per cent.; free hydrochloric acid, 18 per cent. lactic acid negative, faint trace of occult blood.

April 14. Von Pirquet was faintly positive. Upon roentgen-ray examination the stomach seemed pushed to the left, with the shadow of a large mass, taken to be the liver, to the right, indicating a possible involvement of the right and left lobes.

April 15. The nodules in the skin and liver were increasing in size.

April. 16 A roentgen-ray examination of the chest by fluoroscope showed a shadow at the left apex suggesting either fluid or a solid growth into the lung.

April 18. Dr. Stengel noted no localized area of fluid at the left apex. The percussion note was dull posteriorly on the left, extending down below the angle of the scapula, and was becoming more marked. Auscultation anteriorly revealed breath sounds bronchial; posteriorly fremitus diminished, breath sounds distant, and tubular with bronchophony.

April 19. The patient was seen by Dr. Martin, who suggested a probable secondary carcinoma of the liver, lung, and spinal cord, with the primary focus in the sigmoid or cecum.

April 21. Ptosis of the left eyelid was marked. The blood showed hemoglobin, 27 per cent.; red blood cells, 3,300,000; white blood cells, 4000.

April 23. The abdominal nodule was removed.

April 25. The glands were noted enlarging on both sides of the neck.

April 27. Microscopic report on the nodule was made by Dr. Speese. The majority of the cells, cylindrical in shape, are infiltrating a stroma, suggesting sarcoma, but their type resembles carcinoma of glandular origin.

April 28. The patient had three convulsions of the entire body, Jacksonian in type. The right side of the face was involved, the tongue protruded to the right, next both upper extremities and body, and finally both legs, especially the right. During the convulsions the body was blue, afterward became red, followed by right-sided unilateral sweating. A spinal puncture was made at this time; the pressure was 40 mm.; the fluid dropped 140 times per minute. The blood-pressure now was systolic 140 and diastolic 75 on the right side, systolic 130 and diastolic 85 on the left side. During the attack the patient was unconscious, with a heart rate of 145.

April 19. Patient was unconscious and now had a right-sided hemiplegia. The blood-pressure was systolic 115 and diastolic 60. A spinal puncture resulted in no fluid. The eye-grounds were negative.

April 30. The patient died. The temperature was normal or subnormal, and never higher than 99° until this morning, when it went up to 100°, and just before death to $100\frac{3}{5}°$. The respirations ranged between 20 and 25 until April 28, when they went up to 28 and on up until at death they were 40. The pulse averaged 110 until April 28, when it went up to 160, corresponding to the rise in temperature.

Autopsy Protocol. J. M., 4485, 14–89, died April 30, 1914. The autopsy was made at the University Hospital a few hours after death. The body is that of an adult white male about fifty years of age. General amaciation is marked, not unlike that of the pictures of cholera patients without the septic facies. The pupils are slightly dilated and equal. The conjunctivæ are cloudy, especially at the angles. The teeth are still present in fair shape, with considerable sordes, and the mucous membranes are pallid.

A tumor mass is palpable on the right radius midway between the elbow and the wrist. Upon preliminary incision the abdominal wall is less than one-half inch in thickness; the adipose tissue has entirely disappeared. The musculature is dark and greatly atrophied.

In the abdomen the liver extends four fingers' breath below the costal margin. On its under surface there is a firm inflammatory adhesion which extends to the white line of the transverse colon at the hepatic flexure. This has produced a distinct constriction. Fom here the transverse colon has a well-marked midline ptosis, the angle being down in the pelvis. Beyond this the transverse colon becomes smaller (up to this point it has been dilated) and the entire descending colon is small and contracted. The small intestine is contracted, and much of it puddles in the pelvis. The cardia of the stomach extends well down; near the pylorus it makes a sharp kink to the right, the pylorus thus coming to lie below the head of the pancreas, crossing the transverse portion of the duodenum, causing the first and second portions to be greatly distended.

The liver (Fig. 2) weighs 2400 gms., and measures 27 x 22 x 9 cms., the organ is generally pallid, with blotchy areas of blue. On the surfaces, both the superior and inferior, especially of the right lobe, there are seen numerous raised white masses, sharply defined and varying in size from 5 mm. to 4 cm. Some of these masses have central depressions with radiations toward the periphery. Upon cut section the masses are seen to extend throughout the liver structure, one large one being 6 cms. in diameter. These masses have central necrotic areas which are soft and drip away on section. The liver structure is pallid, lobular markings very poorly defined. The gall-bladder is small, contracted, and not in any way connected with the tumor mass. It contains about 5 c.c. of a dark viscid bile. Bile ducts are patulous.

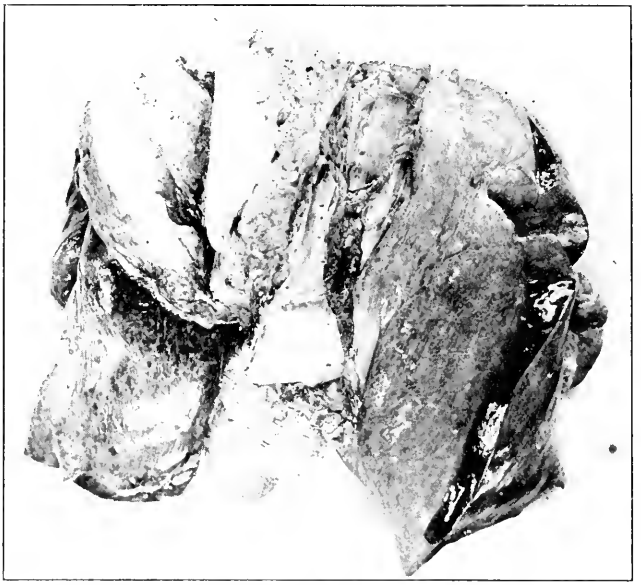

FIG. 1.—A posterior view of both lungs, heart, tumor, and aorta. The tumor is one large mass occupying the apex and posterior portion of the left lung. (Original.)

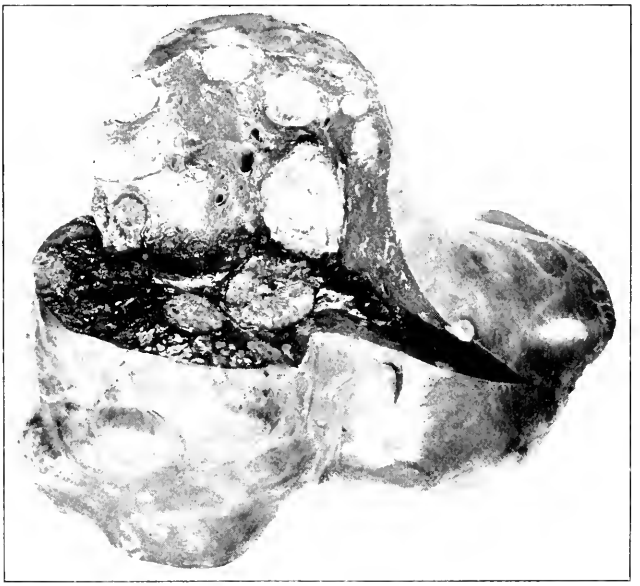

FIG. 2.—The liver is studded with nodules of various sizes showing all the characteristics of metastatic tumors. (Original.)

The stomach contains several hundred cubic centimeters of a greenish, liquid content. The stomach wall is thin, the vessels injected with blue blood. On opening it the rugæ are easily flattened out. There is present an excess of mucus with a general submucosal injection.

The walls of the small intestines are thin; submucosal injection is moderate. The lower part of the ileum contains hard fecal masses, and in this part the mucosa becomes dark and blue.

The pancreas measures 21 cms. in length and is correspondingly broad and thick. The organ is pale yellow. Upon section the lobules are fairly definite, and there is a good deal of bright yellow color to them.

The left adrenal is small and firm, and has a very little fat about it. On section it shows a dark medulla and a yellow cortex.

A small retroperitoneal lymph node lies in close relation but is not adherent to it.

The left kidney weighs 220 gms., measures 13 x 5 x 4.5 cms.; the organ is firm, pale blue, cuts with ease, and the cut edge bulges. The capsule strips without much difficulty; is adherent but does not tear. Upon section the surface is blue, especially so at the upper portions of the pyramids. The darker portion of the latter has considerable fibrous tissue, which sends parallel interlineations into the cortex. There is a fine granularity to the cortex upon reflected light.

The right adrenal resembles its fellow on the opposite side.

The right kidney weighs 210 gms., and measures 13 x 6 x 3 cms.; the organ resembles its fellow on the opposite side, except that it shows more of the blue color. Upon section of this kidney there is one small mass, 2 mm. in diameter, which upon section looks like a secondary tumor mass.

The urinary bladder contains 50 c.c. of a light amber urine. The bladder wall is thin.

The spleen weighs 125 gms., and measures 11 x 6.5 x 3.5 cms.; the organ is soft. The capsule is wrinkled and shows no secondary involvement; cuts with ease; the splenic pulp is mushy; trabeculæ and follicles are not prominent.

The pleural cavities are free from fluid and show a few adhesions at the base on the right side. The left apical portion of the pleura (Fig. 1) contains a mass measuring 14 cms. in length and 11 cms. in thickness. This is a pale mass of tumor material which has apparently sprung from the pleura and is growing downward over the upper lobe and between the pleural surfaces of the upper and lower lobes of this lung. Toward the midline it surrounds the arch of the aorta for a distance of 10 cm., and this is constricted so that one finger is admitted with difficulty into the lumen. Posteriorly the tumor erodes the vertebræ, so that it is possible to place the index finger into the spinal canal. The third rib at its union with the vertebra is eroded and fractured. Many of the mediastinal lymph nodes are enlarged, some the size of a large walnut; one large one

lies in close relationship to the trachea, the lumen of which it has narrowed.

The left lung has a dark bluish color, more blue in the dependant portion, and has a boggy feel. Upon section, frothy blood-tinged fluid exudes. Just beneath the tumor in the upper portion of the lower lobe there is a triangular raised area, which upon section is dark and granular, presenting a line of lighter demarcation.

The heart was removed in the mass with both lungs and the tumor. The pericardium contains 50 c.c. of a clear serous fluid. The heart is small, rather distinctly bronzed, with remnants of the subepicardial fat along the coronaries and the septæ. The coronary

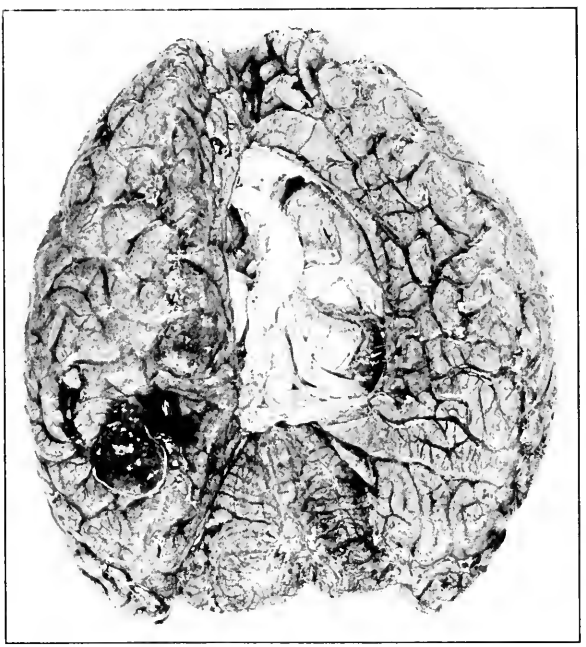

Fig. 3.—The brain presents a small nodule on the convex surface of the left cerebrum just behind the paracentral lobule. (Original.)

vessels are engorged and blue. The epicardium shows numerous white lines of thickening. The left ventricular wall measures 1 cm. The musculature is pallid and soft, and there are streaks of yellow here and there. The aortic valvular orifice measures 7 cm.; valve leaflets are thin, with some adhesions at the angles. The mitral orifice measures 9 cm.; valve leaflets are thin except at the attachment of the chordæ tendinæ. The latter are thin and lengthened out and the papillary muscles short and thin. The right ventricular wall measures 3 mm. and the tricuspid orifice 14 cm.; the leaflets are thin. The pulmonary orifice measures 7 cm.; the leaflets are thin.

The aorta has lost its elasticity; there is some thickening in a wavy fashion to the intimal surface. The constriction noted above is in the descending arch just beyond where the vessels pass off.

In the brain (Fig. 3) the dura over the middle portion of the upper surface of the left hemisphere in the midline is adherent to a mass 3 cm. in diameter, which has evidently arisen from the dura, pushing the brain substance ahead of it. In this growth in the cerebrum the mass has undergone considerable softening.

The spinal cord shows no lesion grossly at the position of the erosion through the vertebral column. Apparently neither involvement of the spinal meninges nor of the cord is present.

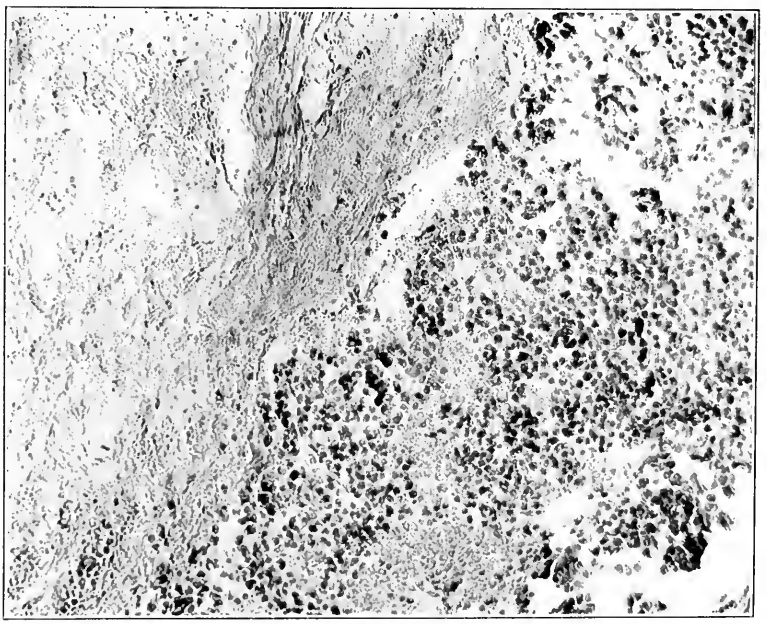

FIG. 4.—The section includes the tumor springing from the surface of the thickened pleura. A large endothelial type of cell occurring in masses with necrosis of central groups. (Photomicrograph, original.)

The following tissues were prepared and submitted for histological examination: lung, pleura, tumor and bronchus, peribronchial lymph node, heart, aorta, liver, spleen, pancreas, adrenals, kidney, stomach, mesenteric lymph node, and tumor of the forearm.

1. In a section of the lung taken from the dependant portion, hemorrhage, congestion and edema is very marked. There are no areas of necrosis in this, so that infarction is ruled out. An exudation of cells, mostly polynuclears and fibrin, is marked throughout the section. Collections of large endothelial cells of the phagocytic type, containing dark brown pigment of hemosiderin, are seen.

Another section from the lung shows a fibrous pleural surface, the

alveolar walls thin, spaces in places collapsed, in others widely dilated and rupturing into one another. There is a moderate anthracosis in this part of the lung. Here (Fig. 6) the spaces are filled with a small amount of exudative material, desquamated alveolar cells, some round cells, and large numbers of phagocytic cells containing hemosiderin. Some of the spaces have dense masses of tumor cells. A large bronchus, which is dilated, shows desquamation of its lining cells, and contains a moderate number of polynuclears and tumor cells. All of the vessels are congested, and some of the smaller ones have ruptured.

2. A section through the tumor mass (Fig. 4), including the pleura, shows a more active proliferation of the cells of the pleura than elsewhere, with extension of these cells along the alveolar walls, forming a new fibrous network. In a section of the pleura, including the tumor and aorta, the tumor is seen to be made up of a considerable growth of fibrous network, which is actively proliferating along with the tumor growth. This coarser network runs out into a finer fibrillar structure, leaving spaces which are filled up with tumor cells. There is one definite type of cell running through all the sections of the tumor. It is round, in places it is lengthened out and looks like a columnar cell. In other places it is flattened out and looks like a plasma cell; it has a moderate amount of acid-staining cytoplasm and a centrally placed nucleus dark and hyperchromatic or light and vesicular. Karyokinetic figures are not well seen. The cells in places group in masses, forming a syncitial type. Where they are round or similar to columnar epithelium they seem to be following the lines of embryonic vessels, so that the arrangement of hyperrephroma is suggested. A mass of well-stained cells often lies in immediate juxtaposition to a group of cells which are necrotic. A moderate number of round cells of the lymphocytic type are intermingled with the tumor cells. In places the cells seem to line spaces as though they were trying to carry out their normal function. Where the tumor mass is close to the aorta it has infiltrated the adventitia and stopped at the median coat. This portion of the aorta shows a loss of the fibro-elastic tissue both in the intima and media, with replacement by a loose type of fibrous tissue. In the intima degenerative changes of a fatty nature have taken place.

3. In a section of tumor and a large bronchus (Fig. 5), one makes out the mucosal lining of epithelium in places thinned and desquamated. There has been a slight submucosal injection and fibrosis. The glands show a moderate catarrhal change, with the presence of goblet cells and mucin in their lumens. At the fibrous union of the cartilaginous rings the tumor cells are attempting to penetrate. If ulceration occurred at this point they might readily get through and continue to grow along the bronchus. Beyond the line of the cartilage the perichrondrium is somewhat thickened and the tumor mass may be seen growing against it—well defined, however, by the density of its tissue. The tumor has penetrated as far as it

can against the cartilage. The same type and grouping of the cells are seen, with the exception that there is not the extensive necrosis as seen in the primary tumor.

4. The peribronchial lymph node shows an increase in original fibrous tissue. The infiltration by the tumor is wide-spread throughout the node, especially the central part.

5. In the heart the epicardium is thin. The section has not included a milk plaque. The subepicardial fat is decreased. The coronary vessels are injected and show throughout some thickening of their walls. There is a very slight increase in the fibrous tissue of the intermuscular septæ. The cardiac muscle has lost a good deal

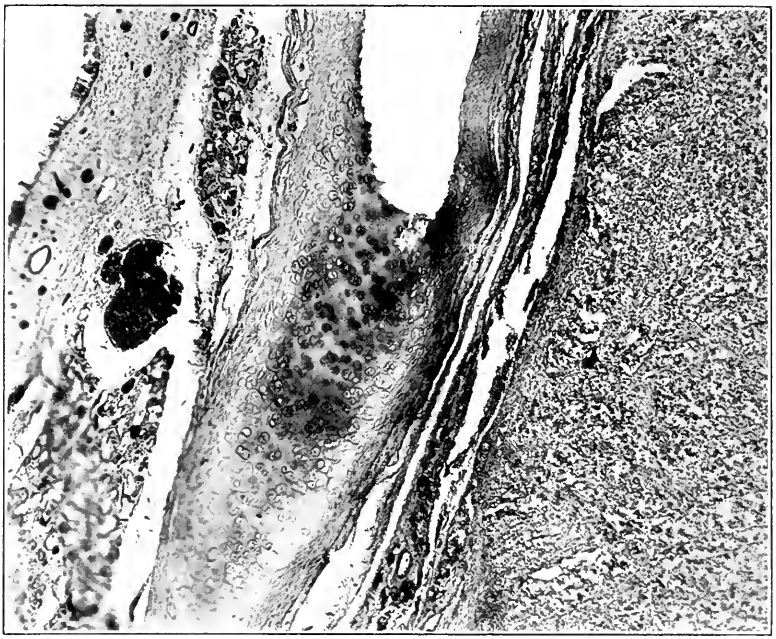

FIG. 5.—To the left of a cartilaginous ring of the trachea is the congested mucosa with swollen and desquamated epithelium; to the right the tumor has grown up to the perichondrium. (Photomicrograph, original.)

of its structure, the fibers being thin, pale staining, and fragmented; the striations are poorly defined; numerous small vacuoles are present, the nuclei are mostly small and pyknotic, and there is very little tendency to a deposition of myohemoglobin.

6. The aorta, taken from the abdominal portion, shows the changes described above in connection with the tumor. If there is really any change, fibrous replacement here is more marked and there is a general contraction of the coats, so that the width of the aorta is relatively less than usual.

7. In the liver there is a tendency for the structure to be open, due probably to fixation. Many of the red blood cells in the section have

been washed out, leaving the dilated vessel spaces. Congestion has been more marked about the central lobular veins than elsewhere. Here the liver cells are filled with the brown pigment of hemosiderin. These cells are small. The nuclei show clearly, the protoplasm is granular and pale staining, and contains multiple small clear-cut vacuoles. In the periphery of the lobules the condition of turbidity and granularity may be still made out, but the vacuolization is not as prominent. A third section was taken in connection with the tumor growth. In this the tumor is more or less sharply outlined—not so much by fibrous tissue as by a condensation of the liver cells. Here the cells are compressed closely together—they are small, filled

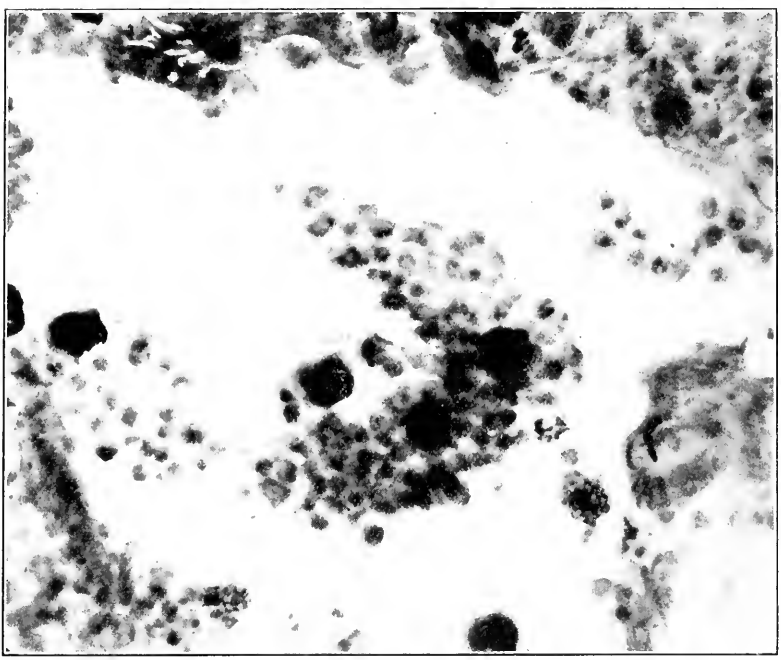

FIG. 6.—The contents from the alveolus of the lung, polynuclear, leukocytes, lymphocyte, phagocytic endothelial cells, and tumor cells. (Photomicrograph, original.)

up with a large amount of pigment, and many of them are vacuolated. The tumor in this situation takes on very strongly the characteristics of epithelial cells, the cells being attached by the base along the lines of fine embryonic bloodvessels. Their nuclei are very vesicular and karyokinesis is more often seen. In some places where these new bloodvessels have been cut transversely the cells are more of the plasma type. The same tendency to necrosis in the center of these masses is present, as in the parent growth.

8. The spleen shows the capsule slightly thickened, irregular and faint staining; the trabeculæ are not prominent. The Malpighian bodies are small and there is a tendency to hyalinization of the coats

of the central arterioles. In the general splenic structure there are a few pulp cells; congestion has been marked, many of the red blood cells appearing as ghost corpuscles. The deposition of a golden-brown pigment is excessive throughout the section.

9. In the pancreas, from the gross description, one might expect to find considerable fatty infiltration, but such is not the case. The lobules of the pancreas are widely separated from one another and the spaces are empty; presumably this was fluid. The general interstitial matrix is thin and fibrillar in character. This same looseness and edema is noticed in the lobules and between the individual acini. There is a tendency for the pancreatic cells to take the stain in different ways; some of these fail to take the stain at all, and may be due to fixative faults. These cells, however, are quite brown in color, suggesting the blood-staining of passive congestion. In the basic stain they appear small and compact, with the nucleus poorly defined and fragmented. The islands of Langerhans are loose and consist of few cells.

10. In the adrenals the capsule is thin; fibrous tissue trabeculæ are not excessive. The zones of the adrenal are well-marked and the cells take on different characteristics, so that one gets the appearance of openness throughout. Most of the cells are pale staining and show vacuolation described in the cortical susbtance. When the cells show protoplasm this is acid-stained and fragmented; the nucleus is small and pyknotic and the chromaphilic property of all the cells, even those which are very badly vacuolated, is very marked. This section suggests in its varied pathology that if the organs of internal secretion play any part in the tumor formation an example is here present.

11. The kidney shows the capsule thickened, loose and edematous, with a tendency to penetrate. Congestion of the cortex, moderately advanced, is present throughout. The glomerules show the spaces of Bowman dilated, capsules thickened, glomerular tufts decidedly thickened, compact, and containing many nuclei. The secreting tubules are distended, the individual cells are in a state of granularity, and have been flattened out against their basement membranes. In other words the tubular cells are small but show a marked grade of cloudy swelling. The protoplasm of the cells in places is badly fragmented and possibly vacuolated; some loss of protoplasm is evident in the collecting tubules. The fibrous tissue of the pyramids is not increased but the spaces are open and filled with edema. One of the glomerules seems to be filled up with a small clump of tumor cells—at least the cells correspond in character to those seen in the sections of tumor.

12. In the stomach the thinness of the wall as described grossly is quite apparent. This is due to a loss in the muscular coat and the openness due to fluid in the submucosal coat. There is a moderate injection of the submucosa and rather marked injection of the mucosa. The mucosal lining is separated from its submucosal

fibrous tissue. The epithelial cells of the mucosa show varying degrees of goblet formation, with the lumina filled up with acid-staining mucus.

13. The mesenteric lymph node shows the same tumor formation as characterized the peribronchial lymph node.

14. A section taken from the tumor in the forearm shows a bit of the voluntary muscle along one side, with the characteristic development of the tumor in the nodule. The same fibrous tisssue network, the same islands of cells, and the same necrosis as described elsewhere. In the brain a small mass imperfectly globular, protruding to the surface on the median side of the left hemisphere just behind the paracentral lobule, friable, is about the size of the end of the thumb. When a horizontal section is made through the hemisphere this mass is found entirely loose in the brain substance, where it lies in a cavity. It does not extend to the lateral ventricle. A piece contains a clot. Endotheliomatous cells in groups are found close to the clot.

The following diagnoses are made from the autopsy protocol: A primary endothelioma of the pleura with extension to the lung, metastases to the mediastinum, liver, kidney, lymph nodes, skin, right radius, and dura. The lungs: chronic fibrous pleuritis, passive congestion, hypostatic congestion edema and pneumonia, anthracosis, atrophy with atelectasis and compensatory emphysema. The heart: chronic fibrous epicarditis, chronic parenchymatous myocarditis with atrophy. The arteries: chronic fibrous panarteritis. The abdomen: chronic fibrous peritonitis (bands). The liver: passive congestion, chronic parenchymatous hepatitis, including cloudy swelling, fatty metamorphosis, and hematogenous pigmentation. The spleen: passive congestion with atrophy. The pancreas: atrophy with edema and parenchymatous degeneration. The kidney: passive congestion with chronic parenchymatous nephritis. The adrenals: chronic parenchymatous adrenalitis. The stomach: chronic atrophic catarrhal gastritis. The skeleton: erosion of the vertebræ and third rib with fracture of the latter and erosion of the radius.

In the correlation (Fig. 7) of this case one is quite able to study, with a considerable degree of satisfaction, the course of the disease. The duration was approximately one and a half years. Serious symptoms were present over a period of a year, with a progressing intensity. The primary growth gave the cardinal symptoms of lung involvement, cough, expectoration, and dyspnea. Terminally the objective signs are easily explained by the solid mass. The roentgen-ray shadow is interesting. The metastases developed their symptoms, especially the brain mass. The negative eye-grounds are explained by the size of the mass. The condition of the stomach might in itself explain the vomiting, but many such types are encountered at autopsy when vomiting was not present. The constipation is easily accounted for by the condition of the intestines if one looks

at it from the stand-point of intestinal stasis. This, too, may explain the early headache; the fixation of the left vocal cord by the involvement of the recurrent laryngeal nerve; unilateral sweating by the

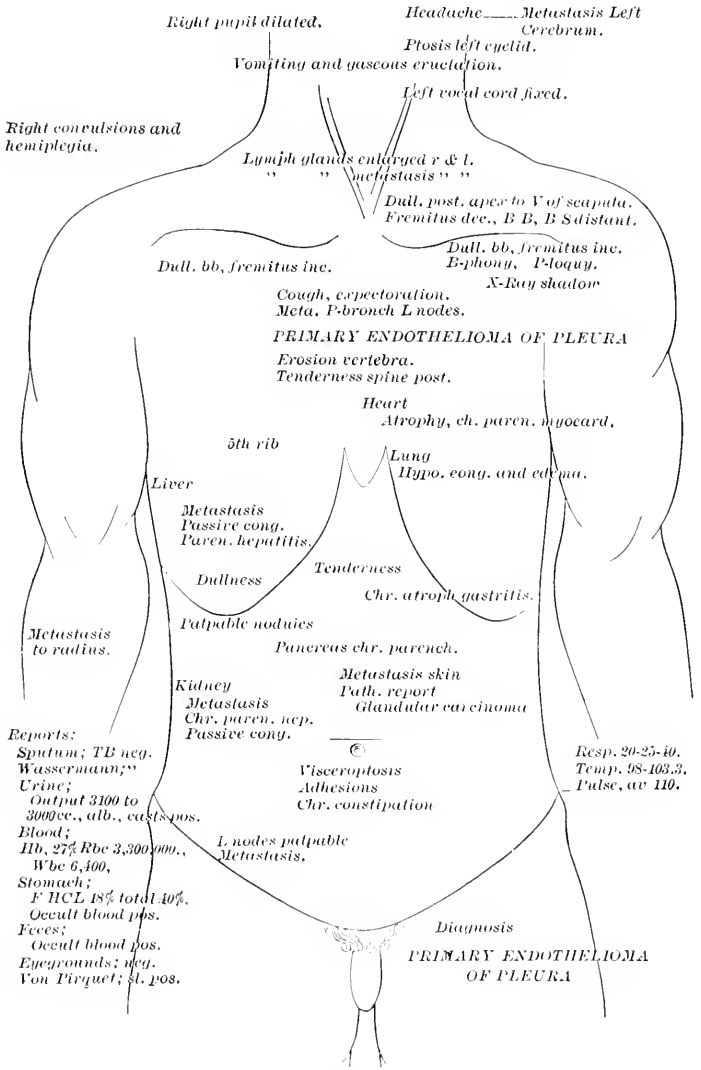

FIG. 7.—A graphic chart of the clinical signs, symptoms, and reports, with the corresponding autopsy findings. This method of presentation is specially useful for teaching purposes using lantern slides.

involvement of the sympathetics and the tenderness over the spinal region posteriorly by the erosion of the vertebræ and rib are readily explainable. The passive congestion was produced by the pressure

on the vena cava and the myocardial changes, while the pressure on the aorta resulted in a marked constriction. Under ordinary circumstances one would expect to find at least some evidence of a left-sided hypertrophy of the heart, and it may be said, I think correctly, that the factor nutrition lacking in this case not only did not permit an hypertrophy but actually was in part responsible for an atrophy. The presence of a mucopurulent sputum with a negative tubercle bacillus would seem to be especially significant.

From the pathological point of view we are dealing with a primary growth of considerable size, showing wide-spread yet slow multiple metastases. In studying these slides I cannot get away from the idea of an association of this tumor with a specific inflammation. The types of cells, their great individual variation, their groupings with a tendency to necrosis, marked evidences of simple inflammation, all lead me to one idea that this pathological complex has many of the features of a specific inflammation. The cells group themselves in places much like glandular epithelium; in these parts connective tissue is profuse. In other places large groups of cells collect in masses with almost no connective-tissue framework. Here often blood channels are made out of the cells and large areas are necrotic. The cells in the metastatic nodules are more characteristic of the endothelial type, but here the gross lesions very closely resemble carcinoma, as in the liver. On the other hand the brain nodule might have been a primary tumor arising from the dura.

From a study of the types of cells found in the bronchi I would suggest the possibility of making a tentative diagnosis clinically from the examination of the sputum.

Conclusions. 1. Primary endothelioma of the pleura is relatively rare and from the literature occurs as a single tumor or as multiple nodules. Progressive loss of weight, dyspnea, and fluid in the chest are the most common symptoms. The tumor shows an endothelial type of cell with epithelial groupings hence, often, the name endothelial cancer.

2. Clinically this case was of seventeen months' duration. The patient presented loss of weight, weakness, cough, expectoration, headache, vomiting, gastro-intestinal symptoms, chest signs of consolidation, roentgen-ray shadow over the primary growth, metastases, palpable lymph nodes, palpable liver with nodules, fixation of the vocal cords, negative sputum and Wassermann, and secondary anemia. The case terminated in a nephritis, cardiac failure, Jacksonian convulsions, and hemiplegia.

3. Pathologically there was one large primary mass arising from the pleura, composed of endothelial cells in various types and arrangements, with extension to the lung, bronchial lymph nodes, trachea and bronchi, and compression of the aorta. Metastases followed to the liver, kidney, lymph nodes, abdominal skin, right radius and brain, with erosion of the spinal bony column and fracture of a rib.

REVIEWS

A Manual of Pharmacology, Adapted to the 1916 U. S. Pharmacopœia, and its Applications to Therapeutics and Toxicology. By Torald Sollmann, M.D., Professor of Pharmacology and Materia Medica, Western Reserve University, Cleveland, Ohio. Pp. 901; illustrated. Philadelphia and London; W. B. Saunders Company, 1917.

This volume, the product of a careful compilation of innumerable references and facts established clinically and experimentally, affords an excellent source for either reference or study. It is, indeed, an ambitious undertaking and one commensurate with the extensive development of theoretical and practical pharmacology. A great mass of minute details are presented, far too great, in fact, to memorize; but their presentation is clear and concise and where points are still in dispute, recent studies by various workers are briefly offered, the decision of the correct interpretation of the points at issue frequently being left to the reader. The references, especially to the recent literature, are well selected and numerous, as is revealed by an unusually extensive bibliography at the end of the book.

As the author states in the preface, it has been his purpose to present, without confusion, the broad conceptions and generalizations, as well as the detailed conclusions comprised in pharmacology. With this end in view, the nature of the book is as follows—large print is interspersed with small, the former giving a connected and concise statement of the essentials of pharmacology as offered by any good text-book on the subject, while the latter, *i. e.*, the small print, contains more detailed data for consultation and is replete with references to the literature. The liberal use of side headings is a distinct advantage.

In revising the text-book of pharmacology, the enlargement required the separation of the laboratory guide in pharmacology which has appeared as a companion volume. This separation offers several advantages at once apparent to the reader. The discussion of the many drugs of slight importance has been curtailed, more space thus being left for the fewer drugs of greater value.

There are no numbered chapters in the book, the first part of which is allotted to the elementary principles of pharmacology,

following which a general discussion of the treatment of disease is offered. Next the various drugs in their respective groups are considered, the space allotted to each being governed by the importance of the drugs discussed. Aside from those arranged in groups, a great many other drugs of minor import are briefly described. Certain portions of the text of the United States Pharmacpœia are inserted. At the back of the book will be found an appendix presenting a tabulation of average doses, a check list for the study of preparations and an extensive bibliography.

This volume has a large sphere of usefulness not only as a textbook, but also as á reference to the pharmacological literature.

A. H. H.

The International Medical Annual, 1916. Pp. 735; 66 illustrations. New York: William Wood & Co.

It would seem that too much has been attempted for a book of this size. To attempt to mass together the important literature of a year on all branches of medicine is, of course, an enormous undertaking. Certain subjects are considerably slighted, notably pediatrics. The war has greatly diminished the output of ordinary European medical work, although it has resulted in much writing on war surgery. This is thoroughly covered in the *Annual*. The reviewer believes that if books of this type are used at all they should be separate volumes on definite specialties. A. G. M.

A Laboratory Guide in Pharmacology, Adapted to the 1916 U. S. Pharmacopœia. By Torald Sollmann, M.D., Professor of Pharmacology and Materia Medica, Western Reserve University, Cleveland, Ohio. Pp. 355, illustrated. Philadelphia and London: W. B. Saunders Company, 1917.

This book, a companion volume of the author's *Manual of Pharmacology*, has for its purpose the familiarization of the student with the more important facts of pharmacology by way of observations obtained at first hand in the laboratory. The volume is divided into two parts. Part I is devoted to the essential features necessary to the medical student and includes a series of pharmaceutic and toxicologic exercises arranged for a course of thirty working periods of two to three hours. Part II consists of a series of experiments on animals, affording a direct means for the student to observe the pharmacologic action of the more important drugs.

The problems of impaired functions are thus introduced and their correction by therapeutic agents suggested.

Additional optional experiments are offered. The arrangement of the exercises throughout is clear cut and concise. Introductory remarks, explanatory notes, numerous illustrations and diagrams add to the value of the book to the student. For the instructor, several features contribute to its usefulness, among which may be mentioned the systematic arrangement throughout, the technical references and the contents of the appendix at the end of the book.

A. H. H.

THE HEALTHY GIRL. By MRS. JOSEPH CUNNING, M.D., and A. CAMPBELL, B.A. Pp. 190; 23 illustrations. London: Oxford University Press.

THE attempt of the authors is laudable, "To help the girl who is leaving school and learning to face life, to understand the most important circumstance she is likely to encounter herself." To a certain extent a growing girl might read this book with profit, although it is written in a manner which would be more capable of interpretation and benefit to mothers and teachers.

Elementary anatomy and physiology are entered into, in order to explain the nervous system and digestion; as well as the bad effects of posture and lack of exercise. There are chapters on Work and Rest; Fresh Air and Breathing; Bad Habits; The Open-air School and Menstruation. In the chapter on Teeth the authors go a little too far, or rather are perhaps not sufficiently discursive, when they leave the impression that all osteo-arthritis, gout, neuritis, etc., are due to pyorrhea and decayed teeth. The statement is made that neurasthenia is due many times to unhealthy condition of the gums and teeth. The reviewer is of the opinion that in a book ostensibly written for the lay public, it would be better not to make statements such as the above, unless they are qualified.

Altogether the book is readable, although not remarkable, and may serve a useful purpose. A. G. M.

MODERN METHODS OF TREATING FRACTURES. By ERNEST W. HEY, the Bristol General Hospital, etc. Pp. 286. New York: William Wood & Co.

THE interesting introductory chapter entitled the Myths of Yesterday and the Problems of Today deals with general considerations of fracture treatment and emphasizes the disadvantages of

treatment by immobilization alone as formerly practised, and states that the modern problem is to secure perfect joint action and to preserve the full vitality of the circulation and neuromuscular apparatus. The keynote of the book is the author's aim to show that as occasion requires there should be brought into service the newer methods: (1) massage and mobilization, (2) extension methods, and (3) operative methods rather than to regard them as rival systems. His method of double transfixion offers a distinct advance in extension treatment. An excellent chapter on operative treatment is based upon experimental work done by the author with the assistance of grants made by the Science Committee of the British Medical Association. After describing the technic of operative treatment as applied to patients he deals with certain special fractures, with due attention to mechanical accuracy and efficiency.

The illustrations of the results of experimental work are especially commendable. The book is written in precise style and with convincing clearness. It is worthy of careful reading by experienced surgeons, since it is indeed "modern," and is based upon a large amount of clinical and experimental study. G. M. L.

Candy Medication. By Bernard Fantus, Professor of Pharmacology and Therapeutics, College of Medicine, University of Illinois. St. Louis: C. V. Mosby Company.

Those who are called upon to treat children often encounter the child who refuses medication. Again, some drugs are obnoxious to any child. Dr. Fantus tells us how to give many drugs (indeed, many more than most of us will use) in an attractive and palatable manner. The method of preparation and dispensing as described is not difficult, and is well worth while knowing. The book contains a rather elaborate formulary. A. G. M.

A Manual of Surgical Anesthesia. By H. Bellamy Gardner, Honorary Anesthetist of the King George Hospital, etc. Second edition. New York: William Wood & Co.

The author has in part rewritten this book for the second edition and has added several new chapters. He gives a history of anesthesia, a chapter on cardinal principles in which he emphasizes the importance of avoiding anaxemia and properly makes this the keynote of the entire volume. In subsequent chapters the phenomena of anesthesia are fully described and considered from the standpoint

of physiology so that the method employed may be selected with reference to the type and temperament as well as the pathologic condition of the patient. He gives an adequate description of the more important general anesthetics and the apparatus for their administration. The chapter on spinal anesthesia is too brief to be of much value. There are many useful hints for dealing with certain special operations. The volume is fairly well illustrated and is printed in large type. It is written for the student and practitioner and is especially to be recommended to dentists, since the author has paid particular attention to the technic of anesthesia for dental operations. One could take exception to the practice of touching the cornea to observe the corneal reflex as being unnecessary and dangerous. The work is essentially a practical treatise based on accurate observation and large experience. G. M. L.

Epidemics Resulting from Wars. By Dr. Friedrich Prinzing. Edited by Harald Westergaard, Professor of Political Science in the University of Copenhagen; Member of the Committee of Research of the Division of Economics and History of the Carnegie Endowment for International Peace. Pp. 346. Oxford: At the Clarendon Press, Humphrey Milford.

The stated purpose of the Division of Economics and History of the Carnegie Endowment for International Peace is to "promote a thorough and scientific investigation of the causes and results of war." Its members consist of statesmen, publicists, and economists. At a conference of this division in Berne, Switzerland, in 1911, thirty-seven questions and problems were drafted for extensive investigation, and it is stated that these are to be "discussed scientifically, and, as far as possible, without prejudice either for or against war." It is not obligatory that the members of this division shall make these investigations themselves, but that they shall select competent collaborators who shall present reports in the form of books or monographs. These reports must be read and edited by a member of the division, and are published upon his recommendation.

The monograph under review treats of the results of war from a point of view that is quite interesting to medical men and one that has not been sufficiently emphasized before. It shows that until recent times the greatest cost of life in war has not been from fatalities in battle or from disease among the soldiers, but from epidemics among the civil population. Emphasis is placed upon the epidemics associated with the Thirty Years' war and their important part in Germany's prostration afterward, the deaths from typhoid, smallpox, and dysentery in our civil war, the smallpox

epidemic following the Franco-German war, and the death rate in besieged cities, as Paris, where it was in 1870–1871 three times normal, and Port Arthur. Until comparatively recent times the plague and typhus were the most common of the pestilences of war, although cholera, dysentery, typhoid fever, and smallpox have contributed largely to many mortality lists.

The work is scientific, good reading, quite interesting historically, and is the statement of another point against war. T. G. M.

Nerve Injuries and Shock. By Captain Wilfred Harris, R.A.M.C., Physician to St. Mary's Hospital, London. Pp. 127. London: Oxford Med. Press.

This book is written for the physician, rather than for the surgeon. It is of particular value to him who has to deal with cases of nervous exhaustion, neurasthenia and functional paralysis of various kinds. G. M. L.

Surgery of the Head. By Major L. Bathe Rawling, R.A.M.C., Surgeon and Senior Demonstrator of Operative Surgery, St. Bartholomew's Hospital, London. Pp. 150; 31 illustrations. London: Oxford Med. Press.

The subject of head injuries is covered in a clear and practical description of applied anatomy, symptomatology of the various traumatic lesions, and the generally approved methods of treatment. The chapter on operative technic could have been amplified with advantage. Present-day warfare demands particular attention to the surgery of the jaws and orbit, and the author could have described more fully some of the work that is being done in this field with brilliant results. G. M. L.

Malay Poisons and Charm Cures. By John D. Gimlette, M.R.C.S., L.R.C.P., Residency Surgeon of Kelantau, One and Protected, Malay States. Pp. viii, 127. London: J. & A. Churchill.

This little book is a materia medica of the remedies and destructive poisons employed by the native "medicine men" of Malay and particularly of Kelantau. With his descriptions of the various medicaments and charms the author has given the local superstitions and translations of some of the native incantations. J. H. A.

INDEX OF 458 POSTMORTEMS OF THE INSANE. NUMBER 1181 TO 1638. By CHARLES J. SWALM, M.D., and ABRAHAM L. MANN, M.D. Volume II.

THIS is the second volume of indexes of the autopsies of the insane in the State Hospital for the Insane at Norristown. It is interesting as a statistical study of brains and some spinal cords in the various types of insanity. In Part II there is a valuable index of different brains in the various types of insanity and a classification of anatomical lesions other than those found in the brain and spinal cord. T. H. W.

NOTES ON THE CAUSATION OF CANCER. By the HON. ROLLO RUSSELL. With a preface by Dr. DAWTREY DREWITT. Pp. 116. London: Longmans, Green & Co.

THIS book, published by the author's wife and issued posthumously, is a continuation of Mr. Russell's statistical studies, particularly in the direction of food consumption, a subject in which he shows a strong leaning to vegetarianism. He starts out with a premise that there is no single cause of cancer but that irritation and injury are the causes. The injury may be mechanical or toxic, and he lays great stress upon local injury, as in pipe-smoker's lip cancer or tar-worker's skin tumors. The burden of this work, however, is to show that the principal causes of cancer are alcohol, tea, coffee, excessive eating, condiments, sour food (vinegar, wines, and cider), very hot food and drink, putrefying food, and, last and least, parasites.

The arguments supporting the contentions are stated flatly and without submitting them to a critical analysis, although there is a considerable show of seeming analysis. The book is not a great addition to the literature of neoplasms, as the methods used are perilously near those of the unreasoning protagonist. H. F.

MODES OF RESEARCH IN GENETICS. By RAYMOND PEARL, The Maine Agricultural Experiment Station. Pp. 182. New York: Macmillan Company.

IN this little book of five chapters is reprinted material which the author has brought together from a number of sources to meet the needs of those who have found merit in the original presentation and desire to make use of the methods and conclusions in their teaching. The subjects thus considered are the current modes of research in

genetics, biometric ideas and methods in biology, nature of statistical knowledge, problems of inbreeding, genetics and breeding. The compilation is timely and would be very useful to any one concerned in the study of any biological problem where statistical methods are used. Rarely would the medical man find application for the methods elaborated, but many conclusions have their significance for him. McC.

Psychology and Mental Diseases. A Hand-book of Psychology and Mental Diseases. By C. B. Burr, M.D., Medical Director of Oak Grove Hospital (Flint, Michigan) for Mental and Nervous Diseases. Fourth edition, revised and enlarged, with illustrations. Philadelphia and London: F. A. Davis Company.

In this small volume the author has approached the subject of mental diseases by the psychological route. It is a revised edition and is intended as a primer for attendants and nurses insofar it should serve its purpose. The chapters on nursing and handling of mental cases are excellent. S. L.

Children. Their Care and Management. By E. M. Brockbank, M.D. F.R.C.P., Honorary Physician Royal Infirmary, Manchester. Pp. 259. London: Henry Frowde, Hodder & Stoughton.

The work belongs to the category of "books for the mother" in which the attempt is made to instruct in the rudiments of nursery hygiene and dietetics.

The author wisely lays little emphasis on disease, but restricts himself largely to a consideration of the needs of the average normal child. Important as is an appreciation of the danger signals of illness, the note of alarm can be struck so loudly as to cause infinite worry to the mother and consequent harm to the child.

In the present volume the instruction is well within the limits of lay comprehension, sensible and reasonably safe from criticism. That all the statements and advice would meet with unqualified approval is, of course, more than could be expected. For the mother who is thrown on her own resources, such a book will prove of real help, but no book can take the place of experience or of advice and actual demonstration by a competent physician or nurse. A. G. M.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
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The Retinitis of Arteriosclerosis, and its Relation to Renal Retinitis and to Cerebral Vascular Disease.—R. FOSTER MOORE (*Quart. Jour. Med.*, x, p. 29, 37–38) reports his studies upon the retinal findings in 44 patients admitted to St. Bartholomew's Hospital suffering from cerebral vascular disease, and 66 cases which came to the Moorfield's Eye Hospital complaining of visual disturbances. The patients from St. Bartholomew's have not been traced, as they were already the subjects of cerebral disease, but 59 of the 66 patients seen at the Moorfield's Eye Hospital have been followed carefully for the development of cerebral vascular lesions. His observations, carried out in minute detail, lead him to recognize three varieties of retinal disease, all of which may occur in the same patient, but which usually appear separately, and have very different prognostic values. These three types of retinal disease are: (1) Retinal arteriosclerosis, in which the vessels of the retina appear tortuous, irregular in the size of their lumina, with obstruction of the blood flow in the veins where they are crossed by arteries, and other signs not so important. Hemorrhages also occur frequently in the retina. (2) Arteriosclerotic retinitis, in which the evidences of retinal arteriosclerosis are present usually in an advanced state, but in which are added exudates into the retina, which appear as small white dots usually scanty in number and often affecting only one eye (45 per cent. of the 31 cases). This is really an advanced degree of retinal arteriosclerlsis. (3) Renal retinitis, in which the arteriosclerotic changes are slight or absent, and large white patches of exudate, with edema and not infrequently detachment of the retina, are

observed. This is the type seen most frequently in chronic parenchymatous nephritis. In the chronic interstitial types the patches of exudate are smaller, the star figure about the macula is more frequent and hemorrhages in the retina are more extensive, while the arteriosclerotic changes in the retina are more marked. The author believes that in renal retinitis there is a toxic element added to the arterial cause of the retinal disease. The large white patches or "cotton-wool spots" seen in this affection never appear in arteriosclerotic retinitis. After a careful analysis of the 110 cases the author concludes that in the group of cases, 35 in number, showing only retinal arteriosclerosis, the mortality is lower, the incidence of gross cerebral vascular disease is less, and the blood-pressure is lower than in the cases, 31 in number, showing the changes characteristic of arteriosclerotic retinitis. Of the 44 cases admitted to the hospital suffering with gross cerebral vascular lesions 30 per cent. had no changes in the retinæ, 27 per cent. showed the changes of retinal arteriosclerosis and 43 per cent. had the characteristic retinal picture of arteriosclerotic retinitis. Thus 70 per cent. of the cases showed changes in the retinal vessels. Following up the cases from the Moorfield's Eye Hospital 27 are known to have died and the cause of death was ascertained in 26, 12 or 46 per cent. of the deaths resulting from a gross vascular cerebral lesion. Forty-six patients from the 66 included in his cases have been followed, and 21 or 46 per cent. are known to have developed gross cerebral lesions. Eighteen of the remainder are still alive so that the above proportion will be added to as time passes. The patients with arteriosclerotic retinitis live longer than the average patient showing renal retinitis, and, as can be seen, the percentage of deaths from cerebral vascular disease is much greater than that in renal retinitis, in which the average death is from "uremia" within about two years. Therefore the author feels that there is a form of retinitis which is associated with severe general arteriosclerosis, is secondary to local retinal vascular disease, and may be only incidentally associated with disease of the kidney, its ophthalmoscopic character, its significance and its prognostic value being largely distinct from the corresponding features of renal retinitis. The cause of death is referable to disease of the vascular system and not of the kidney, and the patients usually live somewhat longer than those suffering from so-called renal retinitis.

Intestinal Protozoa in Salonica War Area.—Lieutenant W. ROCHE, in his report to the Medical Research Committee (*Lancet*, 1917, cxcii, 297) gives the results of 1425 examinations of the stools of 893 cases of diarrhea and dysentery occurring among the troops of the Salonica war area. These cases occurred during the months of August, September and October, 1916, and the author makes the observation that the incidence of diarrhea and dysentery is proportional to the number of flies, decreasing during cold weather and very hot, dry weather during which times the flies are also diminished greatly, and increasing again as the flies increase in warm, moist weather. In the 893 cases nonpathogenic amebæ were found in 81 cases, and amebæ which were not identified because of lack of time in 39 cases. Entameba histolytica was found in 37 cases; Emtameba minuta in 47 cases. Flagellate protozoa were found in 217 cases divided as follows: Lamblia intesti-

nalis, 73; Tetramitus mesnili, 90; Trichomonas, 45; Cercomonas, 9. Coccidia were found in 18 cases. The author states that the bacillary dysenteries were predominant types, and observes that the comparatively few cases of acute amebic dysentery were interesting in view of the fact that many of the troops present in the Salonika area had been either in Egypt or Gallipoli and were Entameba histolytica carriers. The amebic cases were treated with 1 grain of emetin administered hypodermically every day for twelve days. The coccidia usually disappeared from the stools in a few days, but the lamblia and tetramitus infections were the most difficult to get rid of. Calomel, bismuth, salol, turpentine, thymol, emetin and Dale's double emetin were given by mouth with no result, and rectal irrigations with quinin, turpentin and eusol were also without effect.

SURGERY

UNDER THE CHARGE OF

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The Practical Application of the Wassermann Test in the Diagnosis and Control of Treatment of Syphilis.—Craig (*Am. Jour. Syph.*, January, 1917, p. 192) says that the figures here given and the conclusions arrived at are based upon the results of 35,000 Wassermann tests personally performed and that the same technic has been employed in making all of these tests with the exception that, during the past two years, cholesterinized antigens have been used as well as antigens prepared from syphilitic fetal livers. As a result of his studies of these cases in the army the following deductions are made concerning the interpretations of the results of the Wassermann test: If the diseases, other than syphilis, that sometimes have given a positive result with the Wassermann test, can be excluded, a double-plus (four-plus of some writers) reaction is diagnostic of syphilis. Under such conditions, Craig considers this type of reaction as absolutely specific, whether symptoms are present or not, or whether there is or is not a history of infection. Under the same conditions, a plus reaction (three-plus or two-plus of some writers) may, in primary, tertiary, and latent infections be regarded as diagnostic, provided there is a clear history of infection, or suspicious clinical symptoms are present. In the absence of either history or clinical symptoms a plus reaction should not be regarded as diagnostic of the disease. A diagnosis of syphilis should never be made upon a plus-minus reaction. Many perfectly normal individuals give this type of reaction and it is of no value in the diagnosis of the disease except that it should be considered as negative. A single negative reaction, where there is no history of infection and where symptoms are not present, is of considerable value as a corrob-

orative sign of the absence of syphilis, but where there is any suspicion that the disease may be present it has very little value in excluding syphilis. It is only when a negative reaction is repeatedly obtained over a long period of time that it can be considered as good evidence of the absence of syphilis, and even then the spinal fluid should be tested and a provocative Wassermann test should be made after the reaction has remained negative for at least a year without treatment, and if this is negative, the spinal fluid should be tested.

The Advantage of Pyelotomy Drainage for Nephrotomy Wounds.—Keyes (*Jour. Urol.*, 1917, i, 91) says that a tradition has been handed down from the early days of kidney surgery warning us that incisions of the kidney pelvis heal badly. This tradition doubtless had its origin in the slow healing or permanent fistulæ resulting from simple drainage of the widely distended pelvis of a hydronephrotic kidney. During the last decade we have learned that the kidney pelvis heals fully as well as the kidney parenchyma if there is no obstacle to the outflow of urine. On the other hand he has found unexpectedly slow healing in a number of nephrotomy wounds. They have sometimes continued to discharge urine two or three weeks or more, even when there was no very evident obstruction to the outflow of urine. He does not recall, however, any slow healing pyelotomy wounds. During the past six months he has thrice opened the kidney parenchyma for the extraction of stone, and then deliberately inserted a probe into the kidney pelvis, and upon this opened the pelvis widely, inserted a rubber tube there for drainage, and closed the parenchyma by suture. Each one of these cases healed with the promptness characteristic of a pyelotomy. It seems, therefore, possible, not only that pyelotomy is to be preferred to nephrotomy for extraction of stone, etc., when this is possible, but that when nephrotomy is done it may seem wiser to suture the incision in the kidney parenchyma and to drain through a counter-incision made in the kidney pelvis.

Chemotherapy of Mercurial Compounds.—Schamberg and Kolmer (*Am. Jour. Syph.*, 1917, i, 1) say that in the test-tube salvarsan exhibits a greater destructive influence on animal parasites, and mercury a greater destructive influence on vegetable parasites. Salvarsan is a powerful trypanocide and a feeble bactericide; mercury is a powerful bactericide and a relatively feeble trypanocide. Trypanosomes appear to react chemotherapeutically in a similar manner. Medicaments which have a destructive effect upon the former, likewise appear to exert a similar influence upon the latter. There is strong presumptive evidence that chemical substances which are capable of destroying trypanosomes in the animal body, exert a favorable influence in syphilis. Their laboratory experiments on trypanosomes and spirochetes point to a greater selective affinity of salvarsan for the Spirocheta pallida than is possessed by mercury. Mercuric chloride has a much greater organotropic effect than salvarsan; in their experiments mercury was fifty times more toxic for white rats than salvarsan. A group of new mercuric compounds has been prepared by them which far transcend mercuric chloride in their bactericidal power in the test-tube. One new compound has shown itself thirty times more powerful in this

respect, both by the Rideal-Walker and the "antiseptic" test. These new mercury compounds also exhibit a greater destructive influence upon trypanosomes than does mercuric chloride. Some of these compounds have shown a lower toxicity than mercuric chloride.

THERAPEUTICS

UNDER THE CHARGE OF

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The Relation of the Acid-base Equilibrium of the Body to Carbohydrate Metabolism and its Application in Human Diabetes.—Underhill (*Jour. Am. Med. Assn.*, 1917, lxviii, 497) states that the ingestion of large doses of sodium bicarbonate has a marked influence in decreasing glycosuria in severe diabetes, and in maintaining the diabetic individual in a state of comparatively good health and vigor. This effect is ascribed to the neutralization of the exogenous and endogenous acid of the organism. In mild diabetes there is evidence that carbohydrate tolerance may be significantly increased by large doses. Finally, these conclusions are in harmony with experimental facts concerning the relation of acid-base equilibrium of the body to carbohydrate metabolism.

The Treatment of Pneumonia by Optochin.—Chesney (*New York Med. Jour.*, 1917, cv, 234) said that there was no doubt that ethyl hydrocuprein, or optochin, as it is known commercially, exerted a curative action in pneumonia. Optochin is a derivative of hydroquinone and was first demonstrated by Morgenroth and his co-workers, to have a specific inhibitatory action on pneumococci in the test-tube. Wright showed that the blood serum of patients who had received the drug was also bactericidal for pneumococci. In order to determine the time of appearance of the bactericidal action in the blood, specimens of blood were obtained from patients before and after the administration of optochin. The bactericidal activity of the serum was tested by the plate method upon actively growing cultures of pneumococci and the results showed that a bactericidal effect on the pneumococci was obtained if they were given an amount of the drug represented by 0.024 gram per kilogram of body weight for twenty-four hours. The time of appearance of the bactericidal action of the drug was shortened provided the first dose was relatively large and was followed at intervals of not more than three hours by smaller amounts. Thus, for an individual of average size the amount administered in twenty-four hours was 1.5 grams, and during the first twenty-four hours the best method of regulation was to give an initial dose of 0.45 gram following it at intervals of three hours by individual doses of 0.15 gram. During the second period of twenty-four hours the

drug could be given in 10 doses of 0.15 gram. It was best given in capsules. The hydrochloride was much more readily absorbed than the base and hence was to be preferred. The oral route of administration had been found to be more satisfactory than the intramuscular route, since the bactericidal action appeared in the patient's serum much more quickly when the drug was given by mouth. One drawback was the toxicity of the drug. These toxic symptoms are chiefly referable to the ear and eye. In all the cases of pneumonia treated with this drug and reported in the literature, one instance of permanent blindness had resulted and temporary impairment of vision in about 4 per cent. In a total of 786 cases reported in the literature the mortality was about 12 per cent. Leschke has emphasized the importance of beginning treatment early with optochin. He collected from the literature 204 cases treated within the first three days of illness with a result and mortality of 5 per cent., contrasted with 119 cases treated after the third day with a mortality of 21 per cent.

The Treatment of Iritis and other Eye Affections by Parenteral Injections of Protein.—Müller and Thanner (*Med. Klin.*, 1916, xii, 1120) state that a number of different observers have reported beneficial affects following injections of foreign protein in the treatment of various acute and chronic affections. They report in this article their experience with such injections in the treatment of eye infections. They used for the injections 5 c.c. of fresh whole milk, boiled for four minutes. Four cases of parenchymatous keratitis due to inherited syphilis that had failed to yield to specific treatment showed marked inprovement after a single injection of the milk and continued to improve after subsequent injections. The most striking and prompt improvement was seen in 11 cases of iritis. In some of the cases the photophobia and pains disappeared within twenty-four hours and the inflammation subsided after a few injections. Those cases of iritis that were of gonorrheal origin did not show as prompt an improvement. They also describe the effects of the treatment in 9 cases of corneal opacity. The authors claim that the cornea became less opaque after the injections. No effect upon coroiditis, complicating corneal opacity, was noted. Because of its very favorable effect on 1 case of gonorrheal conjunctivitis of long standing they recommend that this treatment should be given a trial in every case of gonorrheal conjunctivitis in adults.

The Action of Digitalis in Pneumonia.—Cohn and Jamieson (*Jour. Exper. Med.*, 1917, xxv, 65) report a series of 105 cases of pneumonia studied by the electro-cardiogram simultaneously with digitalis medication. They found that digitalis given by the mouth has an action on the heart, because changes occurred in the auriculoventricular conduction time and in form of the T wave of the electrocardiogram, just as they do in the non-febrile heart. This conclusion is strengthened by finding that the pulse rate in fibrillating and fluttering cases feel in the presence of fever, exactly as it does in non-febrile cases. The dose and the time required to produce these effects are given and are the same as in the non-febrile cases. The authors conclude that digitalis acts during the febrile period of pneumonia. It produces a beneficial, possibly a life-saving effect in cases of auricular irregularity (fibrillation and flutter).

The Treatment of Diabetes Millitus by Prolonged Fasting.—CUMMIDGE (*The Practitioner*, 1916, xcvii, 414) holds the view that, while Allen's method is the best form of treatment at present available for cases of diabetes millitus of the acute or subacute types, it must not be concluded that it is an easy road to a cure, or that it can be used indiscriminately in all cases in which reducing substances are passed in the urine. Many cases of chronic glycosuria particularly in elderly people, do as well without, as with prolonged fasting, if the protein and carbohydrate of their diet is carefully adjusted to their metabolic capacity, and with much less discomfort to themselves; while cases of pseudolevulosuria improve more quickly when placed on a diet consisting of dextrinized starches and vegetables when there is mixed dextrosuria and pseudolevulosuria. An alternating diet gives good results but a preliminary fast is helpful in controlling the dextrosuria, and is advisable if dextrose is the prominent reducing substance in the urine. Before adopting the treatment by prolonged fasting, it is wise to make sure, therefore, that the patient will not benefit as much or more from some less trying method. The history of the case, the clinical condition, and the results of a complete analysis of the urine, collected for the second half of a forty-eight hour period, during which a test diet of known composition has been taken, controlled by several estimations of the sugar content of the blood and determinations of the alveolar carbon dioxide, should all be considered in arriving at a conclusion. If it is decided that Allen's method is likely to give the best results, it must be borne in mind that the fast is only a preliminary to the more difficult and delicate task of adjusting the diet to the patients defective powers of metabolism and promoting sufficient nourishment to keep him reasonably efficient and comfortable.

The Therapeutic Results of Parenteral Injections of Protein in Eye Affections.—FRIENLANDER (*Wien. klin. Wchnschr.*, 1916, xxix, 1329) reports 42 cases of severe trachoma treated by intramuscular injections of 10 c.c. of milk with marked beneficial effect. The interval between injections was never less than forty-eight hours, and in the more chronic cases that yielded stubbornly to the treatment the injections were four days apart. The injection was almost invariably followed by a chill and sharp rise of temperature, and the succeeding injection was not given until the entire subsidence of this reaction. He reports in detail a few of the typical cases treated on this plan and is convinced that the epidemic of trachoma was promptly checked by the injections.

Diagnosis and Clinical Characteristics of Gout.—PRATT (*Boston Med. and Surg. Jour.*, 1916, clxxv, 925) says that the prompt relief from pain produced by colchicum in gout is so striking that many have asserted that this drug is as specific in gout. It is certainly an aid in diagnosis, as colchicum does not have such a marked effect in relieving the pain in acute rheumatism or in other conditions which may be confounded with gout. Salicylates rarely have any marked effect in controlling the pain of acute gout. The relief from the severe pain of gout by atophan is even more striking than that produced by colchicum. Its value in diagnosis is probably less, as it often is of considerable aid in checking the pains of non-gouty arthritis.

OBSTETRICS

UNDER THE CHARGE OF

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Acidosis in Normal Pregnancy.—Emge (*Am. Jour. Obst.*, November, 1916) has studied 68 cases of normal pregnancy to determine the presence or absence of acidosis. By a chemical method he endeavored to ascertain the carbon dioxid in the blood plasma. The results showed that out of 61 cases 55 had acidosis. In practically all of the cases there was acidosis to some extent, but the degree varied so that in some it was scarcely appreciable. An effort was made to ascertain what causes this condition. It was thought that multiple pregnancy might be responsible, but this could not be proved, nor was the period of pregnancy responsible for the condition, because it was found equally in the first and last weeks. In those patients who retained little food it was not especially frequent. In one case where the patient starved herself there was a marked diminution in the carbon dioxid tension in the blood plasma. In one non-pregnant woman, just preceding menstruation, there was a lessened tension but this became normal or above normal later on. Out of 61 cases of pregnancy only 2 did not show a decrease in carbon-dioxid tension indicating acidosis; one of these was a chronic alcoholic who gave birth to a seven months macerated fetus two weeks before term. In the puerperal state 25 patients were studied. In nineteen the condition of acidosis had disappeared; 1 patient had chronic interstitial nephritis, and the findings did not become normal in this case. The remaining 5 did not regain the normal standard but showed little variation. One patient had preeclamptic toxemia when her blood plasma showed a marked diminution in carbon dioxid tension. Labor was induced. Two normal cases were examined during labor and they showed low gas tension and moderate carbon dioxid deficiency. These and similar studies show that acidosis is present in the great majority of pregnancies in varying degree. Where, however, a marked diminution from the normal is present, the finding is significant and adds to the factors from which an estimate of the gravity of the patient's condition can be made.

The Umbilical Cord and its Complications as a Cause of Infant Mortality.—Young (*Am. Jour. Obst.*, November, 1916) reports the case of a primipara with normal pelvis who had previously a laparotomy for septic peritonitis. The membranes ruptured prematurely and the effort was made to dilate the cervix by inserting a bag. When full dilatation had been obtained pituitrin was given; the head engaged and was observed to markedly recede between the pains while the patient suffered considerably from shock. The occiput was obliquely anterior on the right side. The application of the forceps failed and an axis traction, with the services of an assistant, making traction on the bar of the forceps, succeeded in delivering the child. The patient was markedly shocked during the delivery. On examination the cord was three times about the child's neck and had been tightly pulled by the

delivery. The child was dead. The placenta was on the posterior aspect of the uterus near the fundus. Measurements showed that from the umbilicus to the placental origin there was but 9.5 cm. of umbilical cord. In discussing this paper before the New York Academy of Medicine it was remarked that such complications were not infrequent after the use of pituitrin and that the infant was often born asphyxiated. Shortness of the cord is comparatively rare and when one is less than 50 cm. in length it must be considered abnormal. Cords as short as 37 cm. have been observed. In some cases of short cords violent expulsive pains may deliver the child tearing off the cord at the umbilicus. Hemorrhage may then be controlled by a circular purse-string suture, grasping the vessels and closing over the torn end of the cord. If considerable coiling of the cord can be diagnosed so that delivery through the vagina will result in the death of the child, the indication is clear for Cesarean section. It may be added that the coiling of the cord about the child may prevent a natural onset of labor. In a case under the observation of the reviewer a weak primipara went full term without signs of labor; the phenomena of descent and engagement absolutely failed, and elective section was performed. The cord was found coiled three times about the neck, across the chest, and under the axilla. The delivery of a living child through the vagina would have been impossible. In diagnosing the coiling of the cord about the fetus, a hissing sound faster than the placental bruit, and slower than the fetal heart sound, is strongly suggestive of this complication. When the fetus can be mapped out by palpation a stethoscope placed over the fetal neck may elicit this sound.

Toxemia in Pregnancy after Thyroidectomy.—Kosmak (*Am. Jour. Obst.*, November, 1916) reports the case of a patient upon whom thyroidectomy had been done who was in the pregnant condition. There had been marked nausea and vomiting, with constipation, attacks of nervousness, flushes, and tachycardia. The pulse was small in quality and about 110. The abdominal tumor was that of a five months' pregnant uterus. The patient continued under observation, but a great deal of difficulty was experienced in correcting the nausea and vomiting, and there was much neuralgic pain. These symptoms continued, although the urine was practically normal. With the hope of improvement thyroid extract was given in small doses, but apparently without effect. The condition of toxemia became so pronounced that several weeks before full term an attempt was made to induce labor by introducing the Vorrhees bags. This failed and although the membranes were ruptured and amniotic liquid allowed to escape, labor did not develop. An extraperitoneal section was then done, and just preceding the operation pituitrin was given. When the uterus was incised it was found to be in a state of tonic contraction and the delivery of the fetus was so different that a stillbirth resulted. The patient made a fairly good recovery although there was sloughing in a portion of the abdominal wound. About three weeks after labor the patient's toxemic condition became worse and nephritis developed. On referring to the patient's surgical history it was found that the case was one of adenoma of the thyroid, and the surgeon left what he believed was sufficient of the gland substances to carry on the gland function. The right lobe and the anterior half of the left lobe were removed.

GYNECOLOGY

UNDER THE CHARGE OF

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Imperforate Hymen Causing Symptoms in a Child.—An interesting and rather unusual case of the occurrence of marked obstructive symptoms, due to imperforate hymen, before the onset of menstruation is reported by WIENER (*Am. Jour. Obst.*, 1917, lxxv, 398). The patient was a girl of twelve, admitted to the hospital complaining of difficult micturition and enlargement of the abdomen. She had had to be catheterized a number of times before coming to hospital. On examination, the hymen was found to be imperforate and bulging; there was a median hypogastric mass reaching up to the umbilicus, fluctuating, but not tender. This mass was not reduced in size on emptying the bladder. The preoperative diagnosis was naturally hematocolpos, but on excising the hymen about 30 ounces of thin, yellowish-white turbid fluid was evacuated. The vagina was enormously dilated, with an infantile uterus at its summit. The origin of the fluid was apparently the glands of the endometrium and cervix, which for some reason had been unduly active.

Relation between the Age of the Ovum and Sex.—During ordinary conditions of life it is practically impossible to determine in any large series of cases the exact date of conception, and therefore to determine at what period in the life-history of the ovum it has become fertilized. In war times, however, this becomes comparatively easy, owing to the fact that soldiers are allowed home on leave for a few days at comparatively long intervals, and the time of fruitful intercourse can therefore in many instances be determined with a fair degree of accuracy. A very interesting series of observations upon this point have been reported by SIEGEL (*München. med. Wchnschr.*, 1916, lxiii, 1787), who thinks there is a very definite relationship between the age of the ovum when fertilization takes place and the sex of the resulting individual, fertilization of young ova resulting in the production of females, of more mature ova in the production of males. If we assume, he says, as has been pretty conclusively demonstrated, that ovulation commonly occurs between the tenth and fifteenth day after the beginning of the preceding menstruation, we may consider the ovum as *young* from about the eleventh to the twenty-third day of the menstrual cycle (counting always from the first day of the period); as maturing from the twenty-fourth to the twenty-sixth day, and as *mature* or "überreif" from the twenty-sixth to the ninth day. In a tabulated series of 115 cases in which time the conception could be determined, Siegel found that of conceptions occurring from the twenty-seventh to the ninth day of the menstrual cycle, *i. e.*, resulting in the fertilization of a mature ovum, there were born fifty-two boys and eight girls; of conceptions occurring from the tenth to the fourteenth day, resulting in the fertiliza-

tion of the young ovum of that cycle or of the mature one of the preceding cycle, there were born ten boys and fourteen girls; of conceptions occurring from the fifteenth to the twenty-third day, resulting in the fertilization of young ova, there were born five boys and twenty-six girls. In other words, conception occurring with mature ova resulted in 86 per cent. of boys; with young ova in 84 per cent. of girls, and those occurring at the intermediate period in about an equal division of the sexes. A smaller series of 25 cases, observed by another author and quoted by Siegel, give practically parallel results. These findings are quite in accord, says the author, with facts demonstrated by animal experiments, and well known to breeders of dogs and cattle, who make use of them in the development of their stock.

Chronic Urethral Gonorrhea in the Female.—The great importance of this condition, and the fact that it is frequently overlooked or regarded too lightly, is emphasized in a recent article by BIZARD and BLUM (*Presse méd.*, 1917, p. 46). They point out that it affects chiefly young girls and nulliparæ, infection of the cervix being more common in parous women. It exists in two chief forms: Primary ("l'urétrite chronique d'emblée"): This is not very rare; it manifests itself as a pure urethritis, without other localization of gonococci. It is absolutely symptomless, producing no pain, burning, or abnormal sensation, but a drop of thick pus containing masses of gonococci can be expressed from the urethra. Unless a drop of this pus happens to be present at the meatus at the time of examination, however, the only visible evidence of the condition will be a slight puffiness of the tissues. The course of the affection is protracted; it remains torpid, the gonococcus is very tenacious, and treatment is apt to be required for weeks or months. Secondary: This is even more frequent than the primary form; it is found in women cured of a primary vulvovaginal gonorrhea. It manifests itself as a very slight urethral discharge, coming on two or three months after other condition, and rarely sufficient in amount to stain the clothing. Occasionally this form is painful; and sometimes the discharge is sufficiently profuse to be troublesome to the patient. The characteristic sign is, again, the drop of pus, often secured by the physician only after considerable trouble. The patient must be examined before micturition, and often early in the morning, before the first micturition of the day. In cases where the condition is very chronic, and the deeper portion of the urethra is affected, vigorous and prolonged massage of the latter, starting at its inner extremity and pressing it vigorously up against the pubis, is necessary to bring a drop of pus to the meatus. It may even be necessary to scrape out some epithelial elements from the urethra by means of the platinum loop in order to get material for study. The treatment of urethral gonorrhea in women must be persisted in for a long time, and must be mild. It consists in three chief methods: massage, lavage, and applications. Massage is to be done gently, with the finger inserted deeply into the vagina, always from behind forward, care being taken not to injure the urethra against the pubis. Lavage may be done either with or without a catheter, using potassium permanganate 2.5 per cent., oxycyanide of mercury 1 to 1000, or copper sulphate 2 to 1000. Applications must be made every day, but very gently and cautiously. The

mucosa should never be made to bleed, and the treatment should cause no pain after the patient has become accustomed to it. An oily fluid is used such as pure ichthyol or gomenol, applied with a cotton-tipped applicator. After apparently cured, the patient should be reëxamined at regular intervals to detect any possible recurrence.

OTOLOGY

UNDER THE CHARGE OF

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War-deafness.—Lermoyez (*Monde méd.*, January 17, 1917) in this paper limits his observation to the impairment of hearing due to direct and indirect trauma, the former including immediate injuries to the temporal bone and the latter being limited to the effect of concussive shock upon the perceptive apparatus. Immediate trauma is that which is inflicted directly upon the temporal bone, mediate trauma is an injury to the auditory apparatus consequent upon a damage to the cranium and includes the effect of contusions and blows upon the head, a considerable decrease in hearing or complete deafness, resulting with, or without, fracture of the skull. Under the eventualities of modern war conditions in immediate trauma there is usually the penetration of projectiles or bullets or pieces of shell into the temporal bone and these, so far as procedure is concerned, may be divided into two classes, those in which the projectile is visible at the fundus of the external auditory canal permitting immediate removal, and those in which the penetration is deeper with invasion of the petrous portion of the temporal bone or beyond, in which surgical intervention may be made to follow upon the sequence localizing events, surgical intervention following the evidence of a suppurative discharge from the ear, facial paralysis, labyrinthine or meningeal phenomena. In transverse fracture of the petrous portion of the temporal bone, in the great majority of cases, the lesion is perpendicular to the axis of the bone extending from the posterior to the anterior foramen, involving the vestibule and cochlea, but sparing the middle ear; the organ of Corti is usually destroyed and the auditory and facial nerves may be lacerated or divided and there is, usually, a free persistent discharge of cerebrospinal fluid with concomitant signs of fracture of the skull. The impairment of hearing is usually unilateral, and on the recovery of consciousness after the injury there is usually high-pitched tinitis in the affected ear, dizziness, nausea and static disturbance, the latter symptom being sometimes reliable by lumbar puncture. In the longitudinal injury of the temporal bone the temporal parietal region is especially involved and the line of fracture usually runs parallel to the axis of the petrous bone, opening the tympanic cavity, but not necessarily involving the internal ear except as the result of concussion,

the drum-head is usually ruptured and the roof of the tympanum sometimes fractured. The symptoms vary in these cases from those occurring in transverse fracture, there is free, intermittent and prolonged otorrhagia, the impairment of hearing, at first decided, is frequently fugitive and there is rarely dizziness and facial paralysis, and the danger attending this type of fracture is less immediate to the injury itself than to the effect of subsequent infection and the extension of a suppurative process; the hearing is, as a rule, not irremediably lost unless this may come about later as a sequence of the suppurative process. The first aid dressing as recommended by the author is that of dry cleansing and the plugging of the auditory meatus with iodoform gauze, lavage of any kind being contra-indicated. The consequences of indirect trauma constitute in the opinion of the author the true war deafness. With the approximate bursting of a shell the auditory perception disappears without injury to the petrous bone and without evidnece of cranial impact. In some cases the intensity of the noise partly inhibits the auditory nerve or the actual aërial concussion results in such movements to the labyrinth, as to result in serious lesion in that organ. In actual experience there would seem to be two types of this form of labyrinthine concussion, one mild and the other severe. In the mild form the patient is stunned from the shock of the explosion, there is no pain, he can hear musical sounds, and there is no discharge from the ear. The condition improves in the course of a few days or weeks, under conditions of rest, without treatment and the patient is able to return to duty. In the cases of severe concussion the subject often loses consciousness, on recovery he is often unable to stand, is nauseated, he has variable vertigo, increased by movement of the head or the sight of moving objects; his injury is a major one and he must be transferred to a base hospital. The drum-head under these conditions is sometimes found to be the seat of hemorrhagic spots which suggest the possibility of similar lesions in the labyrinth. The future of the hearing is uncertain and the prognosis in that respect must necessarily be guarded; usually the subjective noises and the vertigo gradually decrease and equilibrium is restored except in the event of sudden movement, while the impairment of hearing, at first partial, gradually becomes more decided. In the great majority of the cases local treatment is advisedly limited to the removal of the foreign objects and such repair of the impacted tissues as may be necessary, dry treatment being usually preferable to moist, antiseptic solutions being usually contra-indicated, it being the opinion of the author that the aurist may be more dangerous than the enemy in the event of his incautious intrusion. A due consideration of the element of time in the determination of the extent of the injury effected by concussion of the auditory apparatus which is urged by the author, is seconded by E. J. Mowre and Piatri in their essay entitled "The Auditory Organ in War Time," published in the *Arch. de méd. et de pharm. militaries*, in the first part of which, entitled Labyrinthism, the authors lay stress upon the necessity of care in the physical and functional examination of the subjects and in that accuracy in recording the history and especially the circumstances of the original causation, which mark the work of the history-taking as done in the French war hospitals, repeated examination, static and auditory, being advocated

as necessary and indispensable for the detection of conscious or unconscious aggravations by the patients or else supplementary to possible omission in early investigations, the expert otologist finding that, in case of an injury to the ear, the importance of the blow or of the shell shock bears an indirect relation often to the auditory and static disorders. Undue precipitancy in diagnosis is deprecated, and a review of each case in six months or a year for a definite opinion is insisted upon.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Studies on Experimental Scurvy in Guinea-pigs. — JACKSON and MOORE (*Jour. Infect. Dis.*, September, 1916, xix, No. 3) studied the occurrence of a peculiar infection in a number of guinea-pigs in the laboratory of St. Luke's Hospital, Chicago, concerning the effect of milk diets on guinea-pigs. The animals appeared partially paralyzed and the muscles and knee-joints were swollen and tender. The diet in addition to green food and water consisted largely of milk from a cow having experimental streptococcal mastitis. Experiments were carried out to determine what factors in the diet were responsible for the condition. Groups of animals were fed on various combinations of food chiefly in relation to milk or milk constituents to test both the production of the disease and its prevention. Experimental scurvy was produced in guinea-pigs by diets of pasteurized, raw, boiled, skimmed and condensed milk, streptococcus broth and milk, milk and green vegetables, thyroid extract and milk, casein and water, oats, and bread and bran. Scurvy was not prevented by adding calcium lactate to milk or injecting it into guinea-pigs on a milk diet, nor did the injection of olive oil have any effect in preventing scurvy in these animals. Those pigs fed on a diet of cream, or of olive oil added to milk, showed a "fat constipation" from the effects of which they soon died. Milk-broth cultures of Streptococcus viridans and Streptococcus hemolyticus, water, lactose water, lime water and goat's milk did not produce typical scurvy in the animals whose diet they comprised. Guinea-pigs living on a milk diet showed, as clinical symptoms, preliminary loss of weight, swelling of the joints, and occasionally hyperemia of the gums. Fractures of the long bones near the epiphyseal ends and deformities were commonly observed. The most important pathological lesions noted at postmortem examinations were hemorrhages, found in the

muscles, bone marrow, tooth pulp, costochondral junctions and sometimes in the skin and lymph glands, enlargements of the ends of the long bones and swollen lymph glands. Microscopically the earliest lesions which were seen were a slight necrosis and hemorrhage in which coccus-like bodies were frequently observed. The only evidence of inflammation is slight fibrin foundation and the presence of numbers of mononuclear and polymorphonuclear eosinophile cells. The average time for the onset of symptoms with the pasteurized milk diet was nineteen days; with other diets from eleven to nineteen days. The earliest lesion was observed on the tenth, the latest on the twenty-ninth day. The disease was afebrile and produced no great increase in leukocytes. Cultures of the heart's blood from guinea-pigs with scurvy from milk diet were sterile and passage of blood from these animals to normal animals did not produce the disease in the latter.

Trench Fever.—HURST (*Lancet*, October 14, 1916, cxci, No. 4859) states that among the cases of fever occurring in the British armies in France and Salonica, a considerable number existed in which the diagnosis was doubtful and which were designated as pyrexia of unknown origin. In the early summer of 1915, a number of cases of fever in which two periods of pyrexia were separated by a normal interval were recognized and called trench fever. Later, other investigators described cases of the same disease and showed that there are two distinct clinical types of it. The cases only occurred among officers and men living near the trenches and in the personnel of hospitals and it was for this reason that the name "trench fever" was given to it, although actual residence in the trenches was not an essential factor. Many cases of the first type occurred in the armies in France and Flanders early in 1915 and later in the same year, many cases of the second type occurred. Since December, 1915, the disease has also been very prevalent in Salonica where the infection was probably brought from France. Although trench fever resembles paratyphoid fever during the first pyrexial period, although it is of a characteristic relapsing type and although it may simulate malaria in the short sharp attacks, yet blood taken at different periods has always been sterile, the Widal reaction has always been consistently negative and no spirochete or malarial plasmodium has been found in blood films taken during febrile and afebrile periods. McNee and Renshaw found that trench fever could be transmitted to healthy men by intramuscular or intravenous injection of the blood of patients with the disease. The red corpuscles have the same effect but not the plasma and serum. One attack does not protect against reinfection. No fatal cases have occurred so the true nature of the disease remain unknown, although the striking periodic character of the fever, the considerable increase in proportion of large mononuclear leukocytes and the evidence of an intracorpuscular infection suggest a protozoal origin. All the evidence collected as to the method of propagation seems to point to the fact that the disease is conveyed by lice; cold wet and fatigue seem to be exciting causes in a man who has become infected but shows no symptoms. The author states that as the result of his observations he has concluded that the incubation period is from fifteen to twenty-five days. The disease usually begins without any premonitory symptoms

except a feeling of malaise. The patient complains of severe headache, backache and pains in the legs, shivers and often sweats profusely. The onset is sometimes very abrupt; the patient is giddy, shivers and may be very short of breath. He has a pain in his left side and pain and tenderness in the legs, especially in the shins. Leukocytosis is often present and the percentage of hemoglobin is generally about 80 though the number of red corpuscles is undiminished. In the short form of trench fever, the temperature rises rapidly to between 102° and 104° F. and on the third or fourth day suddenly falls. The pulse rate is only slightly increased. In the long or periodic type, the temperature rises to between 101° and 104° F. on the first evening, and the pulse is usually accelerated in proportion with the temperature. This initial attack is variable in duration. All the symptoms disappear with the fall of temperature at the end of the initial attack and the patient is well for from two to ten days. Then the general symptoms reappear although not in so severe a form. Recurrence follows periodically, the maximum temperature always being reached in the evening. The diagnosis can only be made with certainty from a study of the temperature chart but the association of pyrexia with tender shins is very suggestive of trench fever. The possibility of malaria and relapsing fever should be excluded in making the diagnosis. No fatal cases of trench fever have occurred and the patient never seems seriously ill, except occasionally for a short time in the first attack. The total duration of the periodic type of trench fever from the onset to the end of the last attack is usually between four and six weeks. As the disease is probably conveyed by lice, which become infected by biting a patient during an attack, efforts should be made to keep troops free from them. All cases of trench fever should be isolated and the patients' bedding and clothes thoroughly disinfected. No treatment has been found which prevents the periodic return of attacks or which is really effective in overcoming the pain although some relief may be obtained if constipation is prevented by aperients, and hot applications are used for the pain.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Experimental Cloudy Swelling of the Kidney in Rabbits.—The term cloudy swelling is a most indefinite one to the pathologist. As it was originally applied by Virchow the term indicated a swelling and tur-

bidity of a tissue to be recognized in the gross. This appearance has been accepted by the majority of pathologists as an evidence of intracellular change impeding the normal function of the cells. It was subsequently found that certain characteristic changes could be recognized microscopically which were also spoken of as cloudy swelling. Some discrepancy, however, was found in that the naked-eye appearance of cloudy swelling did not always demonstrate the same microscopic picture. The older authors claimed that more reliance could be placed upon the naked-eye characters than the presence of minute cellular change. It is true that autopsy material from human cases does not permit parallel conclusions by the macroscopic and microscopic method. The swelling which is often observed in tissues is not the result of a common cause and the cloudiness is so variable in its character than an agreement in diagnosis is rarely found among different observers. SHANNON (*Jour. Lab. and Clin. Med.*, 1916, i, 541) studied cloudy swelling in rabbits. By various means, removal of the kidney, ligation of ureter, injection of tartaric acid, liver substance, and bacteria, he brought about various changes in the kidney simulating cloudy swelling. He observed that under normal conditions the cells of the kidney tubules contained numerous albuminous granules, which could be stained by various methods and were caused to disappear by the application of alkalies. By the removal of one kidney these granules became more prominent in many of the tubules of the remaining organ. Although the microscopic granulation was thus intensified, the gross appearance was but little altered. On the other hand the injection of tartrates led to a markedly swollen and cloudy kidney in which no increase of albuminous granules could be observed. Intraperitoneal injections of autolysed liver produced a markedly cloudy swelling with the disappearance of the microscopic granules. Under the conditions in which a gross swelling and cloudiness of the organ made its appearance in the absence of a granular deposit in the cells, the process appeared to be the result of edema and tissue disintegration. Acute toxemias led to a disappearance of the normal granules, while suppurative processes attended with emaciation caused an enormous increase in swollen cells. The author found that kidneys with much increase of albuminous granules usually gave a normal phthalein output. This form of cloudy swelling is claimed to be a physiological response to an increase of protein waste products of the blood and not a degenerative change.

Anatomical Lesions in Late Acquired Syphilis.—The wide-spread distribution of syphilis has led to the advice that, when in doubt in diagnosis suspect syphilis. This suggestion prior to the days of the Wassermann reaction had its value but is no longer as forceful. Some discrepancy still exists between the clinical findings and the observations at autopsy in that a certain number of cases do not demonstrate recognizable anatomical lesions even where a positive Wassermann has been obtained. The reverse is also true. SYMMERS (*Jour. Am. Med. Assn.*, 1916, lxvi, 1457) has given an excellent analysis of almost 5000 autopsies performed at the Bellevue Hospital. Of this number 314 cases of syphilis were found. Many interesting points were brought out in this analysis indicating the incidence and distribution of anatomical lesions in acquired syphilis. Evidences of skin infection were

observed 106 times. This figure indicates the frequency of residua of the secondary rash. Lymphoid hyperplasia was only observed in 20 cases, indicating the transient character of the disease in this tissue unless succeeded by interstitial fibrosis. Syphilitic lesions of the caseous system were encountered 48 times, the majority of them involving the bones of the head. The tibia was affected 16 times. The presence of syphilitic processes in the testis is commented upon by the author. Among 171 males interstitial orchitis was found 67 times. In no case was gumma of the testis found. The latter, it is stated, is an unusual syphilitic process, the author having never met with the lesions in several thousand autopsies and but once in a surgical specimen. A characteristic syphilitic lesion of the base of the tongue is emphasized. This lesion consists of an obliteration of the normal surface markings and smoothness and induration of the surrounding tissue. It is spoken of as the smooth or indurative atrophy of Virchow. In a particular series of 623 autopsies acquired syphilis was determined in 75 instances and of this number 85 per cent. presented signs of indurative atrophy of the base of the tongue. In the present series of 314 cases of late acquired syphilis it was recorded in 25 per cent. Lesions of the respiratory tract occurred 35 times. Of these the larynx was involved in 12, the lungs in 12, and the trachea in 4 cases. Evidence of syphilis of the nervous system was observed in 112 of the 314 cases. The liver also was a favorite site for lues, showing its presence 105 times. Hepar lobatum occurred 50 times, the majority of cases occurring between the ages of twenty and fifty. Associated with the liver changes the spleen was enlarged in 32; jaundice was present in 14 and ascites in 11. The highest incidence of the localization of the syphilitic process was observed in the aorta. There were 175 cases of aortitis; or nearly 56 per cent. The arch of the aorta was involved 109 times and in 42 cases the entire vessel was diseased. The combination of thoracic and abdominal aortitis was present 3 times. Aneurysmal dilatation of the aorta was observed 39 times and saccular aneurysm 45 times. The majority of these concerned the arch. In 1 case as many as 8 aneurysms were found in the vessel. The aortic valves were sclerosed in 64 instances, and definitely retracted in 27. In 51 of the 175 cases of syphilitis aortitis the lesion in the aorta was the only manifestation of syphilis. It is also interesting that syphilitic aortitis is not uncommonly associated with lesions in the coronary arteries. This was observed 45 times. Gastric ulcer of syphilitic origin was observed once. The literature contains only 12 other examples of a similar nature. Luetic lesions of the intestine in which ulceration or stenosis was present, was found in 6 subjects. In the entire series of 314 cases of organic syphilis, gummata occurred 65 times. The majority of these were in the liver.

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Apparatus Used in the Treatment of Fractures.*

J. P. Lord, M. D., F. A. C. S., Omaha.

It has been my personal experience and general observation that general practitioners have too meager equipment for the general treatment of fractures. Ordinarily when a doctor has a case in the home it becomes

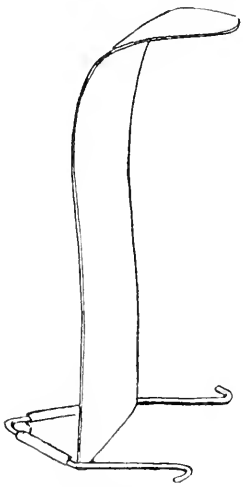


Fig. 4.

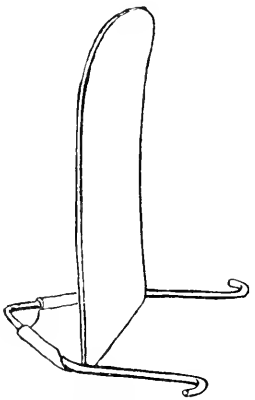


Fig. 5.

Figs. 4 and 5. Extension foot pieces used to avoid toe drop. Width 2½ in., length 5 in. to 8 in.

necessary for him to construct or improvise apparatus for suspension and extension. Some years ago I decided that our hospitals should have something that could be quickly

*Read before The Nebraska State Medical Association, Omaha, May, 1916.

assembled, so that it would not be the surgeon's responsibility to help construct above the bed a device for suspension. I therefore had assembled (Fig. 1) the materials which can be had in any country plumber's shop.

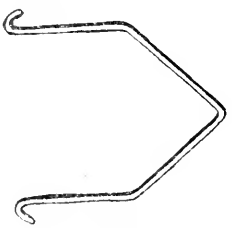


Fig. 6.

Fig. 6. Extension foot piece and spreader to be used with plaster cast and wire No. 7.

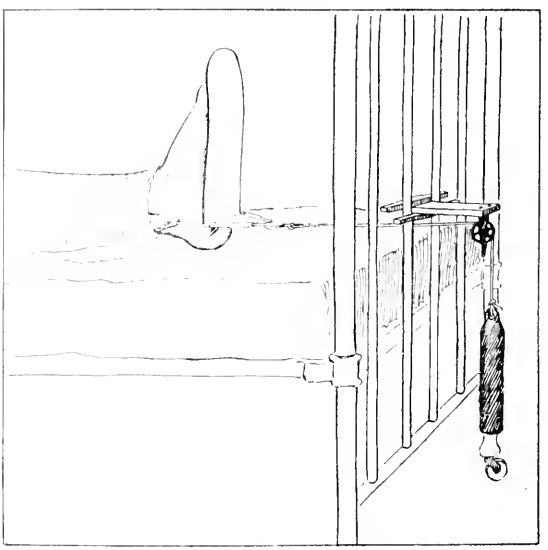


Fig. 7. Shows foot piece applied.

There is considerable leeway in the adjustments, so that it will fit any bed, which makes it a very handy device. It may be taken

apart and be very readily transported. Foot pieces for extension. (Figs. 4, 5 and 6). These can be made by any tinner. Have a series of sizes of window weights, which are marked in pounds, thus you can handily use any amount of weight desired. Some years ago I found it desirable to have some device that would hold up a foot, to prevent the foot dropping while under extension. This is particularly desirable if there is any paralysis or very prolonged extension. The one curved at the upper end holds the bed clothes away from the toes. I had the wire loop made for cases that have a plaster cast, and Buck's extension.

The Special Fracture Committee of the American Surgical Association has reported that most of the bad results in fractures of the leg and thigh are due to inadequate extension. Now, nine doctors out of ten will use ordinary adhesive plaster, and the extension will break down and give way before your case is half over, and it will not permit proper extension any of the time. You should use mole skin and you should use plenty of it. I think doctors should be more particular about the material they use. One of the common faults of adhesive plaster is, that after practically loosened it pulls too much upon small surfaces, and thus produces skin irritation, and possibly blisters.

About twelve or fifteen years ago when we were wiring fractures, I decided that there was too much wiring and other interference —too much carpentering, and that we should

avoid as much as possible the use of foreign materials. I then devised what I call an interrupted loop splint, to be incorporated in

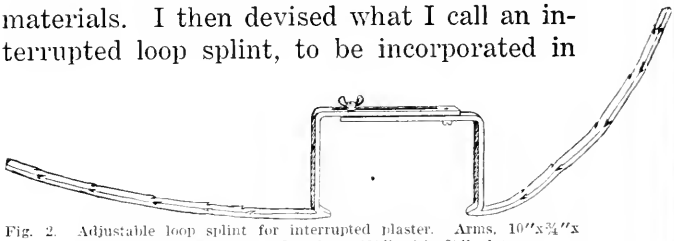
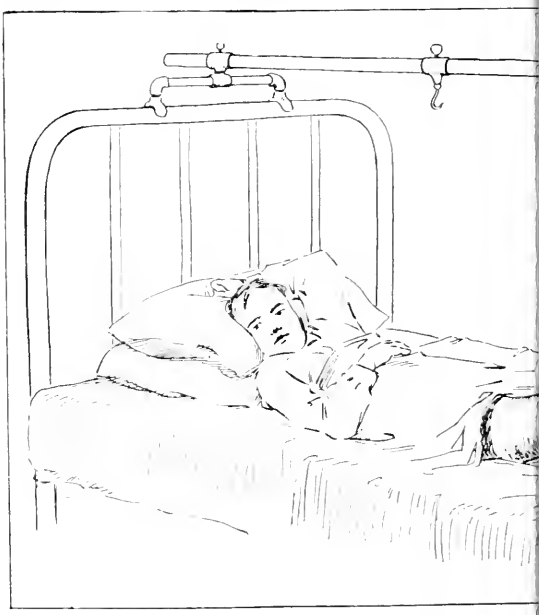


Fig. 2. Adjustable loop splint for interrupted plaster. Arms, 10″x¾″x 3-16″, uprights 3″ long. Crossbars 4½″ with ⅜″ slot.

plaster. (Figs. 2 and 3). This gives you an opportunity to adjust the fracture after you have placed the initial dressing.



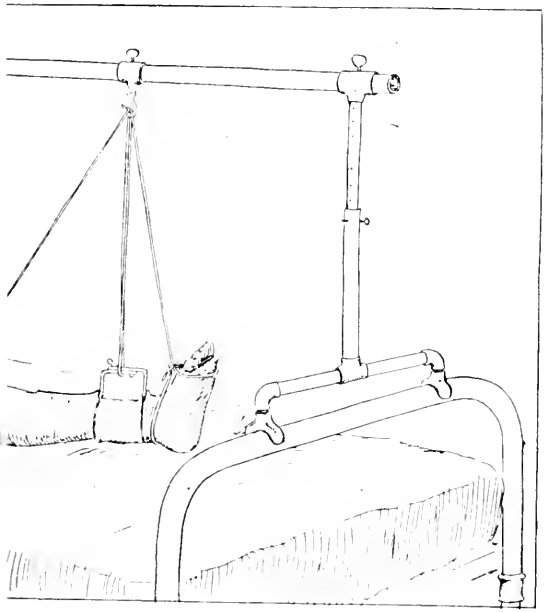
A frame for suspension, made from 1½ in. gas pipe with connecti

Wyeth, some years ago, recommended allowing drills to remain when necessary to hold fragments in place. These are some

specially long drills that I have had made for use in a geared bit stock. They are untempered, except at their points and will not break like the ordinary drill, and are used in the ordinary drill stock. This really answers every purpose of a drill that would

FIG. 3.
Fig. 3. To be used on under side of leg when extra strength is required. Arms 9″x¾″x3-16″. Cross bars 4″ long.

cost ten times as much. Wyeth's drills were made for use in a handle but his apparatus



able to any bed.

is too slow and laborious. In a case of simple or compound fracture, we simply put one or two of these drills through, at a tangent, to

hold the fragments and allow them to remain for ten days or two weeks. We have thus avoided plating. We have not left foreign material permanently in the wound, and we are much more apt to get good results without infection than by plating. Splint (Fig. 2) has been in actual use for a dozen years.

At the Orthopedic Hospital, Dr. Orr, my associate, and myself, have been using a little motor saw and drill, put out by the Pneumatic Tool Company of Chicago, which costs $35. It seems to answer every purpose and runs like a whirlwind; I have never known it to stall. The motor and cord are covered by two sterile muslin slips.

Reprinted from the Nebraska State Medical Journal
Jan., 1917, Vol. II, No. 1, p. 209

Methods Which May Be Employed to Avoid Open Operations for Fractures.*

John P. Lord, M. D., F. A. C. S., Omaha.

The X-ray and modern operative technic has revolutionized the treatment of fractures. Radiography has made necessary approximately anatomic reductions. A perfected technic has supplied the means but its brilliant results have over emphasized the operative side. The failures and disasters are seldom reported, but are nevertheless frequently met. Indeed some surgeons now testify to removing more plates than they put in. The time has seemed opportune, therefore, during the last year or two, for a reconsideration of the treatment of fractures.

The laity is obsessed with the idea that fractures must receive attention immediately. Their penchant for immediate service, from a doctor, causes them to be indiscriminate, oftentimes, in their choice. I sometimes think that doctors have become possessed with these same ideas of urgency. Of course I recognize that attention in reasonable time is usually desirable, but, immediate reduction in simple fractures is seldom actually necessary. Indeed there are many cases in which delay, even for several days,

*Read before The Nebraska State Medical Association, Omaha, May, 1916.

is desirable. The reaction from the trauma is over, swelling becomes reduced, blistered surfaces may be healed, muscle spasm reduced and pain lessened. The anxiety and tension of the patient becomes relaxed and deliberate action may be taken by the doctor. Repeated attempts at reduction may be made within a ten day period, during which time frequent X-ray observations may be made, valuable information gained, and no particular harm done by this amount of delay, and with careful attention to the art of mechanic reduction, success may finally be attained, where less deliberate care and attention to detail, would have rendered imminent the necessity for open operative interference. Many of our best authorities have come to the belief that no fracture, unless compound, should be operated before seven to twelve days.

The people should be made to understand that accurate repositions are frequently impossible by manipulative reductions and that functional results are not dependent upon them. They should also be advised of the uncertainties of results after operative attack, and should be asked to share in its risks. In skilled hands and proper surgical environment the risk is indeed slight, but until there is less promiscuous operating, bad results are sure to be frequent.

It is probable that direct fixation methods, less formidable than plating, such as the more general use of removable nails, staples, and the Hawley, Parham or other clamp, will

more frequently supplant the more deliberate procedures. The use of steel pins, as recently detailed by Foster of New Hampshire, the special drills of Wyeth, and of ordinary finishing nails, used by many (but especially popularized by Murphy), are means of fixation which are simple and efficient in a considerable proportion of cases, especially fractures about joints. Their intelligent use spares many cases from the more formidable open operations, the number of which have been obviously too great in recent years. In this new field, operators with limited experience and inadequate assistance, and facilities, have too often been gaining operative experience at the expense of their patients.

"Zimmerman recalls an eminent surgeon who had devoted special attention to the treatment of fractures and other bone lesions, and at the same time had achieved brilliant results in abdominal and general surgery. Certain of his competitors applied the undesirable epithet to him of "bone surgeon" with the view (as he thought) of detracting from the value of his work in other directions. He remarked at the time, "They will live to see the day when they will be glad to have the title (bone surgeons)." His prediction has come true, for the treatment of bone lesions is today the most difficult of all surgery, requiring a technical skill scarcely known to the abdominal surgeon of twenty years ago, and possessed by comparatively few of the present." (1).

(1) American Jour. of Surgery, Mar. 1915.

The writer ventures to compare the recent furor for operating fractures, to the period when surgeons were making their operating reputations in removing ovaries of only questionable pathology. It requires a decade or two to develop sanity, in the indications and limitations for any operative procedure, among the majority of operators.

Gibbon advocates aiming at overcoming the indications for operative treatment by a perfection of mechanical measures and resources and improving the operative technic of plating when it is necessary.

There is a distinct and unquestioned place for open operations for fractures. Briefly stated, (Zimmermann) the indications for the open treatment are as follows:

(1) In fractures of the shaft of long bones, where reduction cannot be secured by the closed method, or if secured, cannot be maintained.

(2) Where there is interposition of the soft parts.

(3) In spiral fractures of the humerus and femur.

(4) In cases of multiple fractures.

(5) In fracture with marked rotation of the fragment.

(6) Fractures of both bones of the leg or the forearm—in these fractures unsatisfactory results are often-times secured by the closed treatment, and the open method is to be advocated with plating of either one or both bones.

(7) Fractures in or near joints where the fragments or joint surfaces cannot be brought into proper position to secure anatomical alignment and physiological results. Malposition or detachment of fragments, in the region of joints, usually indicates an excessive amount of callus, and the method which will secure the best apposition of the fragments

should be adopted. In many cases this can be better securred by the open rather than the closed treatment."

In highly specialized hands it is a very safe and sure means of securing anatomic correction. Yet there are failures in the best of hands, necessarily. There are too many operative accidents and complications among those limited in experience, and in surroundings, lacking organization, team work, and equipment. Relatively few hospitals are surrounded by an aseptic chain of operating room technic, every link of which is equally strong. The small operating teams doing good work in abdominal surgery, become weak and inefficient in coping with a comminuted fracture of a thick thigh.

When burying foreign non-absorbable material en masse, in the living tissues we are inviting trouble, and it is bound to challenge us in a proportion of cases.

About fifteen years ago the writer, in his teaching and discussions, began pleading for abandonment of the practice of the indiscriminate and frequent use of wire in compound fractures, urged simplicity of procedure and the use of a minimum of foreign material, when used. To carry out this principle "adjustable loop splints" were devised and used, in interrupted plaster casts. These permitted readjustment at any time, without disturbing the plaster. These are especially useful in compound fractures, most of which may thus be treated without the introduction of foreign material. And at

most a ligature of catgut, or a temporary nail.

The use of awl or drill to work into position small fragments or dislocated small bones, has been a resource of value in my hands for several years. In some cases where the extension cannot be made adequate, it would be better for the doctor, inexperienced in operating upon fractures, to do tenotomies instead.

In compound, complicated or irreducible fractures, the attendant should offer the patient the choice of having expert council, being referred to a surgeon, or to be given to understand that he is to bear his share of the burden of responsibility.

There has been a recognized need of crystallized opinion on most of the points in the treatment and handling of fractures. This is evidenced by the very numerous contributions on this subject in recent months. The American Surgical Association has been conspicuous in its efforts in this direction. A symposium covering the various (2) phases of the subject was a large feature at their meeting last year. These discussions gave a distinct note of disapproval of too frequent open operations. Necessity for a more definite working basis in treatment of fractures, has been recognized by many surgical organizations.

The collection of statistics by the British Frac. Com. and the work of the American

(2) Amer. Jour. of Surgery Mar. 1915.

Surg. Ass'n. have revealed a sad lack of detailed reports of hospitals and individuals. Efforts at reform in this, have already been instituted, but until full, accurate, and definite reports are made upon vast numbers of cases, experience tables of value cannot be expected.

Robert Jones in his presidential address on the present treatment of fractures, before the British Medical Ass'n. summarizes these conclusions.

1. "We should be carefully taught the principles governing the reduction of fractures and their correct fixation.

2. We should not be out and out adherents of an operative, a fixation, or a mobilizing school. We should be shown the value of a steady fixed extension in contradistinction to forcible intermittent pulls succeeded by periods of relaxation.

3. Delayed union in a certain proportion of cases is inevitable. Care must be taken not to carelessly relegate such cases to the more serious ununited fractures and insist on plating.

4. Perfection of mechanical methods, lessens indications for operation.

5. Indications for operation differ with the individual stand point of the surgeon, no rules can be laid down. The surgeon with least mechanical resource will operate most frequently."

It may be said that there is now a distinctly greater conservative tendency and if operative procedures are resorted to they are made more simple.

The inlay autogenous bone graft is now perhaps universally employed, by those best informed, in cases of non-union of bone.

Whereas but a few years ago a Lane plate would have been used.

The practice of allowing fractures to drift into the hands of internes and inexperienced assistants, is fortunately lessening. The general surgeons awoke to the importance of fracture treatment during the operative mania for plating everything. Now I think that all are more sane in giving the real detail attention necessary in the successful handling of fractures, and operating only in the exceptional cases in which the necessity for direct attack is obvious.

For years it has been my custom to tell my students and to warn general practitioners that a thigh fracture is of major importance and that those without training and experience should seek skilled help.

The X-ray has properly emphasized the bad work in fracture treatment. It has called attention to a neglected field in surgery. The terms physician and surgeon, so meaninglessly and loosely applied to every graduate in medicine, is an onus borne by us all. The truth is that many doctors are no more fitted to treat fractures than they are to do other surgery for which they are wholly unfitted. The time is not far distant when special qualifications will be exacted of all who do any kind of surgery. The X-ray is beginning to render cautious all who presume to handle fractures.

A discussion of extension before this society is confessedly elementary and even

academic but I feel constrained to state that failure to correct over-riding is most often the result of the inadequate application of this factor in the mechanics of treatment. The grasp of this principle and its proper application would remove the necessity for operations in a very large proportion of the simple fractures in the long bones.

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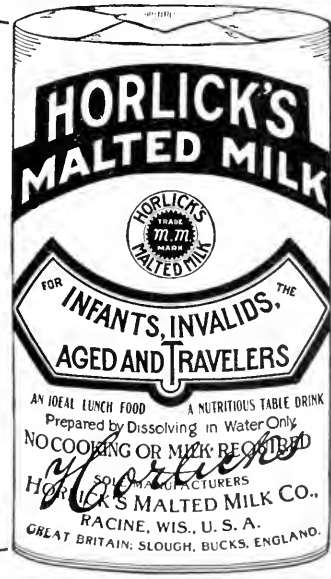

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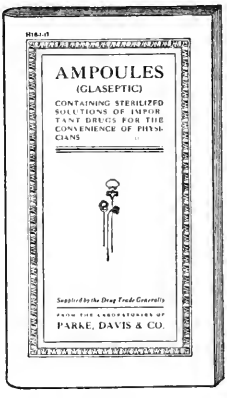

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